

GST
P.B.
JUL 3- 1934

ARCHIVES OF DISEASE IN CHILDHOOD

EDITED BY

CHARLES HARRIS, M.D., F.R.C.P., and ALAN MONCRIEFF, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.

H. A. T. FAIRBANK, D.S.Q., M.S., F.R.C.S.

LEONARD FINDLAY, D.Sc., M.D.

A. DINGWALL FORDYCE, M.D., F.R.C.P.ED.

REGINALD MILLER, M.D., F.R.C.P.

C. MAX PAGE, D.S.Q., M.S., F.R.C.S.

LEONARD G. PARSONS, M.D., F.R.C.P.

G. F. STILL, M.D., F.R.C.P.

HUGH THURSFIELD, D.M., F.R.C.P.

EDITOR OF THE *British Medical Journal*.

Vol. 9.

JUNE, 1934.

No. 51.

CONTENTS

PAGE

Vitamin A deficiency in children.

Part II. Vitamin A requirements of babies : Skin lesions and vitamin A deficiency. By Helen M. M. Mackay, M.D., F.R.C.P.

133

An epidemic of acute encephalitis in young children. By Agnes R. Macgregor, M.B., F.R.C.P.E., and W. S. Craig, B.Sc., M.D., M.R.C.P.E.

153

The aetiology of idioglossia. By I. J. Wolf, M.D.

171

The intradermal tuberculin reaction, with special reference to so-called surgical tuberculosis. By J. W. E. Cory, M.A., M.D. CANTAB.

177

Sensitivity to cow's milk proteins in acute gastro-enteritis. By K. H. Tallerman, M.C., M.D., M.R.C.P.

189

British Paediatric Association : Proceedings of the Seventh Annual General Meeting

195

ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House,

Tavistock Square, W.C.1.

Yearly Subscription (6 numbers), 25/-

Single Number, 4/6

GENERAL ADVISORY BOARD.

H. T. ASHBY (Manchester).
W. R. BRISTOW (London).
ALAN BROWN (Toronto).
E. CAUTLEY (London).
GLEN DAVISON (Newcastle-on-Tyne).
T. V. FINLAY (Edinburgh).
G. B. FLEMING (Glasgow).
Prof. JOHN FRASER (Edinburgh).
Prof. W. E. GALLIE (Toronto).
Sir ARCHIBALD GARRETT, K.C.M.G. (Oxford).
J. F. GASKELL (Cambridge).
G. R. GIRDLESTONE (Oxford).
H. TYRELL GRAY (London).
ROBERT HUTCHISON (London).
R. C. JEWESBURY (London).
F. S. LANGMEAD (London).
C. P. LAFAGE (Manchester).

W. L. MACCORMAC (Balham).
HELEN MAYO (N. Adelaide).
T. P. McMURRAY (Liverpool).
CHARLES MCNEIL (Edinburgh).
A. E. NAISH (Sheffield).
D. H. PATERSON (London).
W. J. PEARSON (London).
F. J. POYNTON (London).
T. G. PUGH (Carshalton).
F. C. PYBUS (Newcastle-on-Tyne).
Sir HUMPHREY ROLLESTON, Bt. (Haslemere).
J. D. ROLLESTON (London).
J. C. SPENCE (Newcastle-on-Tyne).
E. H. M. STEPHENS (Sydney).
G. BRUTON SWEET (Auckland, N.Z.).
C. W. Vining (Leeds).
E. H. WILLIAMS (Dunedin).

NOTICE TO SUBSCRIBERS.

Subscriptions are payable to the Financial Manager of the British Medical Association who has charge of all financial matters concerning the **ARCHIVES OF DISEASE IN CHILDHOOD**. Address: British Medical Association House, Tavistock Square, London, W.C. 1.

NOTICE TO CONTRIBUTORS.

All papers submitted for publication should be sent to Dr. Alan A. Moncrieff, 121, Harley Street, W. 1. All other editorial matters should be referred to Dr. Charles Harris, 31, Weymouth Street, W. 1.

Papers sent for publication should be typewritten. Illustrations will usually be inserted in the text itself, and care should be taken that the text is marked to show the desired position of each illustration.

Charts and curves accompanying papers should be carefully drawn, on tracing linen. Any lettering on these drawings should be lightly inserted in pencil.

Contributors will receive one proof in page, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Contributors will be supplied with reprints of their articles at cost price if application is made when returning proofs. An estimate of costs will be given if desired on application to the Financial Manager of the British Medical Association.

Papers which have been published become the property of the **ARCHIVES** and permission to republish must be obtained from the Editors.

VITAMIN A DEFICIENCY IN CHILDREN

Part II.—Vitamin A requirements of babies: Skin lesions and vitamin A deficiency

BY

HELEN M. M. MACKAY, M.D., F.R.C.P.*

(From the Queen's Hospital for Children, London.)

Do bottle-fed babies require more vitamin A than they are likely to get if no special precautions are taken to provide an extra source of this vitamin? We know that in Great Britain, in the absence of special precautions, vitamin D deficiency is widespread among babies in winter, and vitamin C deficiency may occur on various types of artificial feeding. Of the extent of other vitamin deficiencies in this country, if they exist, we have scarcely any knowledge. At the present time potent vitamin D preparations, prepared by irradiation of ergosterol and devoid of vitamin A, are widely displacing cod-liver oil (which contains both D and A) for the prophylaxis of rickets. Are we thereby running the risk of widespread, if slight, vitamin A deficiency? And what are the signs of slight A deficiency in babies? If either of the names 'growth promoting' or 'anti-infective' vitamin, which have gained wide acceptance, are justified in any special sense, presumably defective growth and lowered resistance to infection would be early symptoms of vitamin A deficiency. The investigation described in this paper was undertaken in the hope of obtaining an answer to some of these problems.

Nature of present investigation.

This investigation, begun in January, 1931, lasted for nearly two years, and was concerned with artificially-fed babies and young children up to 2 years of age living in their own homes. The work was prophylactic. The babies were divided into two groups and conditions for the two groups were kept as similar as possible except in the matter of vitamin A intake. The controls received only what vitamin A or carotene was normally present in the dried milk or 'table food' (i.e. mixed diet) they received. The group with which they were compared received additional vitamin A, both incorporated in their milk and also as an emulsion. The author⁸ in her work on infantile anaemia has shown that the influence of iron deficiency in lowering resistance to infection and retarding growth can be clearly

* Working as a member of the scientific staff of the Medical Research Council.

Part I, entitled 'Present knowledge of the clinical effects of vitamin A deficiency with special reference to children,' appeared in the last issue.

demonstrated by an investigation carried out on similar lines to the present one: hence if these babies suffered from vitamin A deficiency the effects should be apparent. Except in this one point of vitamin A intake the two groups of babies were fairly matched and similarly treated and should provide a definite answer to some of the problems put forward.

Clinical material.

The babies attended the out-patient department of the Queen's Hospital for Children, which is in a poor district in the East End of London. Babies of the poorest social class, children whose fathers were out of work, were intentionally included among the numbers, as it was presumed that any vitamin A reserves obtained by the foetus from the mother would be lowest among such infants.

Number of babies.—The babies numbered in all 171, but of these only 118 were included in the final comparison: 58 of these served as controls, and the remaining 60 were given extra vitamin A, and will henceforth, for the sake of brevity, be called the 'A group.' The 53 children finally rejected from the comparison were excluded for the most part on account of insufficient attendance or insufficient treatment. No child was included who did not attend, and, if in the A group, receive extra vitamin A for at least four weeks. A few have been omitted for other causes; such, for example, as habit vomiting (2 cases), evidence of mental deficiency (2 cases), symptoms of thyroid insufficiency (1 case), or the administration of cod-liver oil by the mother to a control.

Age of infants.—On coming under observation the age distribution of the 118 children was as follows: 65 infants (55 per cent.) were under 3 months old; 45 (38 per cent.) were between 3 and 5 months old; and the remaining 8 (7 per cent.) were between 5 and 7 months old. Thus 93 per cent. of the babies were under 5 months old when first included in the series, the youngest being 29 days. The oldest child at the end of the observation was 25 months old.

Period of attendance.—The period of attendance varied from 4 weeks to $20\frac{3}{4}$ months, and averaged about 8 months (table 2).

Clinical condition of infants.—The majority of the babies were brought to the hospital for underfeeding, or other feeding difficulties, with or without some minor infection such as bronchitis or thrush. Of the rest, a few were patients discharged from the wards after an acute illness, e.g. pneumonia or enteritis, and others attended for such conditions as bronchitis (10 cases), otorrhoea (2 cases), enteritis (2 cases), prematurity or low birth weight (6 cases, 2 with rickets), etc. Nearly all were under normal weight when first seen, and many were in poor general condition, but no baby on first inclusion was seriously ill with any infection. The great majority made good general progress as can be seen in table 2 where it is shown that in the winter of 1930-31 and the summer of 1931 (when the babies were for the

most part young) the weekly gain averaged approximately $5\frac{3}{4}$ to $6\frac{1}{2}$ oz. (163 to 184 gm.) and in the two following seasons (when most of the babies were older, a number being in the second year of life), the weekly gain averaged $3\frac{1}{2}$ to 4 oz. (99 to 113 gm.)

Economic status of families.—The fathers were mostly manual workers. A number were out of work and in receipt of either unemployment allowance or public (municipal) assistance. Out of the 118 families, 26 received a milk grant from the borough, i.e., were in receipt of an income held by the community to be insufficient to maintain health. A further 10 were granted extra nourishment from charitable sources after investigation of the circumstances by the hospital almoner. Thus approximately 30 per cent. were at some time in receipt of additional food from charitable or municipal sources. It is fairly certain that in the face of privation the baby of the family will be the last to go short of any food which the mother realises he requires, and even in the poorest families the child's feeding usually appeared to be in the main according to instructions. On the other hand, as already indicated, there seems a likelihood that the baby may be born with small vitamin A reserves, as the brunt of a poor diet will probably fall on the mother of the family². It should be noted, however, that the parents were not all poverty stricken and included small shop keepers and others in more comfortable circumstances and in regular work.

Attendance of infants.—During the first few weeks of attendance mothers were asked to bring their babies to hospital weekly or even oftener, but once a child was established on its diet, a fortnightly attendance was asked for. Many attended with great regularity. A child who for any reason, other than an infectious fever, was not seen at the clinic for six weeks (even though taking the food prescribed), was counted as having ceased to attend. At each attendance the child was weighed and was examined naked by the author, a detailed record being kept of its clinical condition.

The diet given.

All the babies until such time as they were put on a mixed diet, were given dried milk with added sugar, together with supplements of iron to prevent anaemia, irradiated ergosterol to provide vitamin D and to prevent rickets, and orange juice to provide vitamin C and prevent scurvy. All the A group received additional vitamin A. After the child was 7 to $7\frac{1}{2}$ months old the mother was asked gradually to reduce the dried milk to 1 lb. weekly and concurrently to introduce other food into the child's diet. When the child was 8 to $8\frac{1}{2}$ months old the diet advised was medicated dried milk, 1 lb. packet weekly, fish on two to three days weekly, eggs, 3 or more in the week, and fruit daily, besides milk puddings, bread and other cereal food, vegetables, gravy, broth, etc. The mother was advised to start the child on meat at about 11 to 12 months of age.

Dried milk.—The milk supplied was a roller-process dried milk made by Messrs. Cow & Gate. One advantage of using dried milk and not fluid dairy milk in such work was that by incorporating extra vitamin in the milk and keeping a register of milk packets sold it was possible to know whether or not babies were receiving the vitamin ordered. The milk was that of Devon cows from a Dorset farm. Since these cows supply a milk of high fat content, it was skimmed at the factory and the fat standardised at 3.43 per cent. before drying. To all the milk before drying was added iron and ammonium citrate (31½ grains to each pound of the dried milk), and also irradiated ergosterol to increase its vitamin D value. In addition to the iron and irradiated ergosterol, vitamin A was also incorporated in the milk given to the A group. (For the vitamin values of these additions, see discussion at the end of this section.)

Messrs. Cow & Gate prepared the milk at intervals of approximately 2 to 3 weeks or occasionally 4 weeks, and nearly all the milk was consumed well under 6 weeks from the date of preparation. The two dried milks will in future be referred to as Hemolac + D and Hemolac + D + A respectively.

The dried milk was sold to the mothers at the hospital at cost price. In the case of necessitous families receiving a free milk grant from the borough, it was arranged that the mother should either get milk free through the hospital (the cost being defrayed by the borough), or should get plain dried milk from her borough and exchange it weekly at the hospital for the medicated milk. A record was kept of each packet of medicated milk supplied to a mother, and the quantity used was checked by the feeds ordered for the baby and the packets sold. Up till the age of 7 to 7½ months practically all the calorie needs of the babies were supplied in dried milk and sugar, say 90 to 135 calories daily in sugar and the rest in milk, with the small supplements mentioned. Thus a baby of 9 to 10 lb. body weight probably consumed the contents of a 1 lb. packet of dried milk weekly (equivalent to a little under 1 pint, or about half a litre of fluid milk daily), increasing steadily to about two 1 lb. packets weekly (say 1½ pints, or about 1 litre, of fluid milk daily) by 7 months old. At this age mixed food was started, and the dried milk proportionately reduced, until a child of 8 to 9 months and upwards would be getting about 1 lb. of the dried milk weekly.

Sugar.—The mother was advised to add either 1 drachm (about 4 gm.) or usually 1½ drachms of castor sugar to each bottle feed, i.e., about 90 to 135 calories daily were given in added sugar. Younger babies received a higher percentage of sugar in the milk than older babies, since increases in food were made in milk with no corresponding increase in sugar.

Iron.—A baby getting 1 lb. of dried milk weekly received incorporated in it 31½ grains (about 2 gm.) of iron and ammonium citrate, equivalent to a daily allowance of about 4½ grains of iron and ammonium citrate. Babies on larger milk allowances received proportionately more. When mixed food was given the natural iron in the diet was, of course, much increased.

Vitamin C.—Every mother was advised to give her baby a minimum of one teaspoonful of orange juice daily. Many babies, especially if constipated, were given much larger amounts. From the age of 7 to 8 months other fruit was given.

Vitamin D.—Besides the natural vitamin D of dried milk or 'table food,' each baby received irradiated ergosterol both incorporated in the dried milk and also as an emulsion administered by the mother. This added irradiated ergosterol emulsion, however, was not given during the early weeks of 1931 to the first 17 babies included in the investigation, but was subsequently ordered for all the babies so as to provide an additional source of vitamin D should the mother, by any chance, temporarily run out of the medicated dried milk.

All the vitamin additions were prepared, standardized and emulsified with Irish moss (carrageen) and acacia by The British Drug Houses Ltd., and were supplied in the form of an emulsion both to Messrs. Cow & Gate Ltd., for incorporation in the milk, and to the hospital for dispensing.

The quantities of vitamin D provided were as follows:—

To each pound of dried milk was added before drying 9,800 international units of vitamin D in the form of irradiated ergosterol emulsion, the potency of which had been determined by the line test on rats. Thus if the mother omitted to give any of the extra emulsion a baby of 10 lb. weight would still receive, say, 1,400 international units daily incorporated in his dried milk. In addition to the vitamin D in the milk, babies were ordered 1,050 units of D daily in the form of a separate emulsion (1 drachm—about 4 c.c.—twice daily). If, on first inclusion in the investigation there were any delay in changing the baby from his previous feed on to the medicated milk, the amount of emulsion ordered was increased to 1 drachm three times daily, or 1,575 units per day. Thus, if no vitamin D was destroyed in the process of drying the milk, the total vitamin D supplement would have amounted to, say, 2,450 international units per day for a baby of 10 lb. body weight. This is nominally the equivalent in vitamin D of say 24 c.c., or a little under 1 oz., of a good cod-liver oil daily. In cod-liver oil this is an enormous dose, but some vitamin D may have been destroyed during the drying of the milk, and moreover it seems probable that rat units do not satisfactorily indicate the relative dosage of different substances required for the prevention or treatment of rickets in children^{1, 3}, nor, for that matter, in other young animals¹¹. The amount of vitamin D given prevented the development of rickets in all the children included in the series. That a vitamin D supplement is required by artificially-fed babies in winter is already definitely established, and was, as it happens, also demonstrated by a baby in the series who had been given by the mother only a small and uncertain amount of the medicated milk (with unmedicated dried milk in the intervals) and no extra emulsion, and who consequently developed rickets in April, 1931. He was one of those rejected from the investigation on account of insufficient treatment. No ill effects were observed in any children from the dosage of irradiated ergosterol employed.

Vitamin A in the diet.—The controls received the natural vitamin A contained in the dried milk or 'table food' (i.e., the mixed diet described) only. The A group received in addition vitamin A incorporated in the dried milk and also in the form of a separate emulsion. Thus the control group were given Hemolac + D and an emulsion of vitamin D, and the A group Hemolac + D + A and an emulsion of vitamin D + A. As noted under the heading 'Vitamin D,' the emulsions administered by the mother were not in use during the first weeks of the observation.

The vitamin A concentrate, prepared from mammalian livers, was dissolved in arachis oil, and was standardized and emulsified by The British Drug Houses. There is no doubt that the A group received far more vitamin A than the controls, but to state positively how much more is not possible.

a. **VITAMIN A IN THE DIET OF CONTROLS.**—To begin with let us consider the natural vitamin A content of the milk given to the controls. (Table 1.) Comparatively little information appears to exist concerning the effect on the vitamin A of milk of drying by the roller process on a commercial scale.

TABLE 1.—VITAMIN A VALUES OF THE DRIED MILKS USED IN TERMS OF STANDARD COD-LIVER OILS.

Approximate date estimated.	Cod-Liver Oil Equivalents.		Cod-Liver Oil Standard employed.	Approximate date of drying.	Estimated by.	Method of Estimation.
	Hemolac + D	Hemolac + D + A				
Nov.-Dec., 1930	per lb. 15.3 gm. (a)	per lb. —	12.0 blue value	Nov. 17th, 1930	K. Coward	Biological
Jan.-Feb., 1931	8.7 gm. (a)	29.7 gm. (a)				
14th April, 1931	11.5 c.c. (b)	100 c.c. (b)	7.5 blue value	April, 1931	F. H. Carr	Colorimetric
3rd June, 1931	12.0 c.c. (b)	98.5 c.c. (b)				
26th Sept., 1931	2.09 c.c. (c)	67 c.c. (c)	7.5 blue value	Sept. 10th, 1931	F. H. Carr	Colorimetric
Oct.-Nov., 1931	13.0 gm. (c)	45.4 gm. (c)	12.0 blue value	„	K. Coward	Biological

The letter following the cod-liver oil equivalent of Hemolac + D and Hemolac + D + A indicates the batch of milk; two figures followed by the same letter represent two different estimations of the A value of one batch of dried milk.

Sherman and Smith¹³ give the average vitamin A content of fluid milk as about 2 units per gramme, and of dried whole milk as 16 units per gramme. If these estimations were carried out on milk from the same source before and after drying, they would imply no destruction.

Two sets of figures on the vitamin A content of Hemolac + D are available:—

1. Dr. Katharine Coward generously undertook for the author in the laboratories of the Pharmaceutical Society of Great Britain a biological comparison of the vitamin A content of Hemolac + D and Hemolac + D + A respectively. No simultaneous test on a cod-liver oil was made, but it is possible to give the approximate A value in terms of a standard cod-liver oil by comparing the dose of Hemolac + D which brought about the increase in weight of the rats in this test with the dose of cod-liver oil which brought about the same increase in weight when the curve of response to doses of vitamin A (which is used in the Pharmaceutical Society's Laboratories) was made. Two tests on this sample of Hemolac + D were carried out. The values found by the two tests were:—

(See 'A' in table 1.) Vitamin A value per lb. equivalent to 15.3 gm. cod-liver oil of 12.0 blue value.

(See 'A' in table 1.) Vitamin A value per lb. equivalent to 8.7 gm. of the same cod-liver oil.

This might appear to indicate a loss of vitamin A potency during the six weeks interval between the two tests, but Dr. Coward has shown, by a series of tests of the same sample of cod-liver oil carried out in successive months, that its apparent vitamin A value may show a two-fold variation from month to month. Without simultaneous tests on a standard, she is of opinion that it is impossible to regard the above figures as evidence of deterioration of the Hemolac + D.

About a year later Dr. Coward estimated the value of another sample of Hemolac + D again, for comparison with a sample of Hemolac + D + A. By

comparison with a simultaneous test made on the sample of cod-liver oil mentioned above, the following result was obtained:—

(See 'C' in table 1.) Vitamin A value per lb. equivalent to 13.0 gm. of the same cod-liver oil.

2. Dr. F. H. Carr, of The British Drug Houses Ltd., very kindly undertook a comparison by the colorimetric method. To carry out this test the dried milk was extracted with chloroform, filtered, the chloroform distilled in vacuo and the residue dissolved in chloroform and tested with the antimony trichloride reagent by the method of Carr and Price. Dr. Carr's figures for the vitamin A content of Hemolac + D in terms of a cod-liver oil of 7.5 blue units value were as follows for two estimations carried out on one sample:—

(See 'B' in table 1.) Vitamin A value per lb. equivalent to 11.5 c.c. of cod-liver oil; and

(See 'B' in table 1.) Vitamin A value per lb. equivalent to 12.0 c.c. of cod-liver oil.

The second estimation was made two months after the first. These figures suggest that the A value is well maintained during two months' storage.

Messrs. Cow & Gate kindly allow the author to state that estimations on their full-cream dried milk carried out by Prof. H. Steudel, of Berlin University, support this conclusion. He showed that its vitamin A content was almost unchanged after nine months' storage in closed tins.

Dr. Carr also carried out an estimation on the same sample of Hemolac + D as was last examined by Dr. Coward, and whereas her biological estimation indicated an A content equivalent to 13.0 gm. of cod-liver oil per lb., his colorimetric estimation gave a value equivalent to 2.09 c.c. of cod-liver oil of a much lower blue value. Dr. Carr considers that his figures may be too low as some vitamin A may be destroyed in the process of extraction for the colour test.

It is obvious that there are discrepancies in these findings, but as far as the author is able to ascertain the majority give for reconstituted dried milk vitamin A values of a similar order to those obtained for fresh cow's milk.

The natural vitamin A and carotene obtained by the babies from the 'mixed feeding' given after 7 months of age was fairly liberal. The eggs, fish, dripping, green vegetables, fruit, and, later, meat fat, would all supply vitamin A.

b. VITAMIN A IN THE DIET OF 'A CASES.'—So far we have considered the quantity of vitamin A in the diet of controls. If we consider the vitamin A intake of the 'A group,' we can safely assume that it was at the very least a number of times as great as that of the control group, for they received vitamin A from the same natural sources as the controls, and were given in addition extra vitamin A both incorporated in their milk (Hemolac + D + A) and in the form of an emulsion (Emulsion D + A).

With regard to the milk, Dr. Coward finds by biological tests that Hemolac + D + A contained 3 or 4 times as much A as Hemolac + D when batches of milk prepared on the same date are simultaneously estimated. Dr. Carr finds by the colour test that it contains 8 to 30 times as much when batches of milk prepared on the same date are compared (table 1).

The usual dose of vitamin A emulsion given to the A cases in addition was 2 drachms daily, estimated by Dr. Carr to be equivalent in vitamin A value to 3 drachms (10½ c.c.) of cod-liver oil of 7.5 blue units value. If we accept Dr. Carr's average vitamin A value for the Hemolac + D, we find that the daily dose of 2 drachms of emulsion contained as much vitamin A as about 1½ lb. of the milk given to the controls, i.e., that in one day in the emulsion alone the 'A group' received as much vitamin A as did many controls in a week's supply of milk.

Hence, although it is impossible to make any definite statement in figures as to the relative vitamin A intake of the controls and the A cases, we can safely assume that at the lowest estimate the A intake of the A group was many times greater than that of the controls.

Results.

As will be seen from table 2, the children of the two groups were fairly evenly matched as regards age, sex and weight at the outset of the investigation. The average duration of attendance differed by only a few days, and consequently the average age of the children in the two groups throughout the investigation was similar.

TABLE 2.—THE AGES AND WEIGHTS OF THE VITAMIN A CASES AND CONTROLS COMPARED.

WHOLE PERIOD.	No. of Cases	Sex. M. F.	Average Age.				Average Attendance	Average Weight.				Average total gain	Average weekly gain	
			First Attendance	Last Attendance	First Attendance	Last Attendance		lb.	oz.	lb.	oz.			
A cases	60	40 20	2	24·5	10	28·5	8	4·0	9	2·9	18	12·6	9	4·41
Controls	58	39 19	2	28·9	11	6·4	8	7·5	9	10·4	19	7·2	9	4·43
SUB-DIVIDED BY SEASON														
Winter 1930-31														
A cases	20	13 7	2	28·3	4	18·7	1	20·4	9	9·4	12	4·5	2	5·99
Controls	19	11 8	3	6·9	5	4·4	1	27·5	9	7·1	12	12·2	3	6·46
Summer 1931														
A cases	38	24 14	3	24·3	7	4·1	3	9·8	10	12·9	15	13·2	5	5·63
Controls	36	23 13	3	28·4	7	3·8	3	5·4	11	4·1	16	1·2	4	5·66
Winter 1931-32														
A cases	45	31 14	5	25·2	10	25·6	5	0·4	13	9·9	18	9·3	4	15·4
Controls	42	29 13	5	15·8	10	8·4	4	22·6	13	15·4	19	1·0	5	1·6
Summer 1932														
A cases	31	22 9	9	10·5	12	17·3	3	6·8	16	6·0	19	11·9	3	5·9
Controls	33	24 9	8	20·8	12	15·1	3	24·3	17	5·9	20	13·5	3	3·41

Weight.—The control group averaged 4 days older and $7\frac{1}{2}$ oz. heavier at the outset. If we assume that the normal rate of growth in the third month of life is 6 oz. (170 gm.) weekly, this would imply that age for age the controls averaged $3\frac{1}{2}$ oz. (about 99 gm.) heavier than the A cases at the outset. This slight superiority in weight was maintained, so that the average weekly gain of the two groups was almost identical, namely, 4·43 oz. and 4·41 oz. respectively, a difference of only $\frac{1}{50}$ th of an ounce in favour of the control group (table 2).

If the groups are subdivided by season it will be seen that the seasonal distribution is fair, and that in the smaller subdivisions sometimes one group, sometimes the other shows a slight superiority in rate of gain. Hence we may say that added vitamin A did not increase the rate of growth.

Morbidity rates.—a. **GENERAL.** Morbidity rates were ascertained and compared in the manner already described in the author's work on nutritional anaemia in infancy⁸. The illnesses were counted from the babies' weight charts. Any infection accompanied by a retardation of gain in weight or an actual loss in weight was counted as an illness. Specific fevers (whether or not the baby's weight was available) and attacks of otorrhoea were also counted as illnesses. On the other hand a loss in weight attributed to under-feeding was disregarded. In spite of the subjective nature of such illness counts the author believes that carried out with care they afford fair comparisons.

Reckoned in this way the A group and controls showed morbidity rates which were closely similar as will be seen from table 3. This holds good not only for all illnesses, but also for diseases of the respiratory tract, diseases of the digestive tract and specific fevers when estimated separately. Again if the cases are subdivided by season, a superiority of a small A group in one season is counterbalanced by the superiority of a similar control group in another. (Table 4.) Hence added vitamin A did not reduce the general morbidity rate.

b. **LESIONS AFFECTING SKIN, MOUTH AND EYES.** Lastly, the incidence of lesions of the skin, mouth and eyes was compared in the two groups (table 5). The incidence of eye infections is similar in the two groups. The controls show a slight superiority over the whole period, but this is not constant in the seasonal subdivisions (table 6), and the numbers are small.

Again in lesions of the mouth, the incidence is higher in the A group, but the difference is not uniform over the seasons. In the first two seasonal subdivisions the controls are superior, in the second two seasonal subdivisions the incidence is similar (table 6) and the difference is probably a matter of chance. The actual difference was that in a period of nearly two years 12 more attacks of thrush occurred in the A group than in the controls; there were 19 attacks in the A group and 7 among the controls.

As regards skin lesions an interesting fact is revealed. The incidence of 'infective' lesions of the skin was in the A group approximately half what it was in the control group. The lesions included as 'infective' may for the most part be regarded as due to some form of local irritation with an infection (by local organisms of low virulence) taking temporary root as a result, e.g., sore buttocks, sore scrotal skin or foreskin, intertrigo, dribbling eruptions, etc. Tables 5 and 6 show that each type of infection of the skin included is more common in the controls than in the A group, and that this is so in each of the four seasons under consideration, facts which lend strong support to the view that the difference is significant and not the result of chance. This difference in the incidence of infective skin lesions is the only difference between the two groups which is uniform over the seasons.

If, on the other hand, we examine lesions of the skin with no evidence of microbial infection (urticaria, rough face and sweat rash or erythema), the incidence in the two groups is closely similar all the way through.

TABLE 3.—GENERAL MORBIDITY RATES. VITAMIN A CASES AND CONTROLS COMPARED.

		Vitamin A Cases.			Controls.	
No. of infants	...	60	58
Average attendance	...	8.1 months	8.2 months	
No. of child-months	...	485.6	476.1
Disease.		No. of attacks.	No. per 100 child-months.		No. of attacks.	No. per 100 child-months.
Respiratory tract.						
Cold in head and sore throat		44	9.1	18.5	43	9.0
Bronchitis	...	35	7.2		47	9.9
Pneumonia	...	0	—		1	0.2
Otorrhoea	...	11	2.3		3	0.6
Digestive tract.						
Stomatitis	...	5	1.0	7.8	2	0.4
Diarrhoea & vomiting or either.		33	6.8		34	7.1
Specific fevers.						
Scarlet fever	...	0	—	3.3	2	0.4
Measles	...	12	2.5		9	1.9
German measles	...	1	0.2		1	0.2
Whooping cough	...	2	0.4		5	1.1
Chicken pox	...	1	0.2		0	—
Meningococcal meningitis		0	—		1	0.2
Other diseases		4	0.8		4	0.8
TOTAL	...	149	30.8		152	31.9
Deaths	1	0.2	2	0.4

In order further to test this difference in skin infections between the two groups, the number of babies with infective skin lesions was examined, and in table 7 the number of babies affected is shown, whereas in the previous tables 5 and 6, the number of attacks of infection were counted, and one baby might have had several attacks. When the number of babies was

counted it was found that in the control group of 58 there were 30 children (52 per cent.) who had suffered from one or more infective skin lesions, whereas in the vitamin A group of 60 children the number was only 16 (27 per cent.), i.e., roughly half the number affected in the control group. Dr. A. Bradford Hill, of the Statistical Department of the Medical Research Council, has very kindly examined these figures and concludes that this difference (25 per cent. ± 8.98) is unlikely to have arisen merely by chance since not only is it two and three-quarter times its standard error, but is to be observed in each season.

TABLE 4. GENERAL MORBIDITY RATES. VITAMIN A CASES AND CONTROLS COMPARED : SUBDIVIDED BY SEASON.

	Winter 1930-31.		Summer 1931.		Winter 1931-32.		Summer 1932.	
	A cases	Controls						
No. of child-months	33.6	36.4	126.4	114.4	225.6	199.5	100.0	125.7
	No. of child attacks mths.	Per 100 child attacks mths.	No. of child attacks mths.	Per 100 child attacks mths.	No. of child attacks mths.	Per 100 child attacks mths.	No. of child attacks mths.	Per 100 child attacks mths.
Diseases of respiratory tract	5	14.9	7	19.2	14	11.1	17	14.9
Diseases of digestive tract	1	3.0	1	2.7	10	7.9	10	8.7
Specific fevers ...	0	—	0	—	1	0.8	2	1.7
Other diseases ...	0	—	0	—	1	0.9	3	1.3
Total	6	17.9	8	22.0	25	19.8	30	26.2
					77	34.1	73	36.6
							41	41.0
							41	32.6

If we compare the total number of lesions of the epithelial structures less the 'infective' skin lesions (table 5), we find in the A group an incidence of 16.1 and in the controls of 14.1 per 100 child months, or, as shown in table 7, 63 per cent. of the children in the A group and 57 per cent. of the children in the control group suffered from one or other of these lesions of epithelial tissue. Hence, exclusive of the 'infective' skin lesions, the difference between the two groups of babies is slight.

The findings, therefore, certainly suggest that added vitamin A diminished the susceptibility to infections of the skin, for the difference (1) is statistically significant between the total groups; (2) shows itself both in the total number of 'attacks' and in the number of children affected, so that it is not only a question of some few children having repeated attacks; (3) is apparent in each seasonal subdivision of the total groups; and (4) is

TABLE 5—LESIONS OF SKIN, MOUTH AND EYE. VITAMIN A CASES AND CONTROLS COMPARED.

		Vitamin A Cases.				Controls.	
		No. of attacks.	No. per 100 child-months.		No. of attacks.	No. per 100 child-months.	
No. of infants	...	60	58		
Average attendance	...	8.1 months	8.2 months		
No. of child-months	...	485.6	476.1		
Lesion.		No. of attacks.	No. per 100 child-months.		No. of attacks.	No. per 100 child-months.	
Skin.							
'Infective'—Napkin rashes, intertrigo, external otitis, septic spots etc.		21	4.3		34	7.1	
Dribbling rash	...	1	0.2		4	0.8	
Boils or whitlow	...	1	0.2	4.9	3	0.6	9.7
Eczema	...	1	0.2		4	0.8	
Ringworm	...	0	—		1	0.2	
'Non-infective'—Sweat rash or erythema		4	0.8		9	1.9	
Rough face	...	8	1.6	7.6	5	1.1	8.6
Urticaria	...	25	5.1		27	5.7	
Anus and urethral orifice.							
Anal fissure or sore at urethral orifice	...	4	0.8		3	0.6	
Mouth.				16.1			14.1
Ulcer of palate	...	1	0.2		3	0.6	
Thrush or other stomatitis	...	19	3.9	4.5	7	1.5	2.7
Cracked lip	...	2	0.4		3	0.6	
Eyes.							
Conjunctivitis	...	12	2.5		8	1.7	
Stye	...	3	0.6	3.1	0	—	2.1
Blepharitis	...	0	—		2	0.4	

VITAMIN A DEFICIENCY IN CHILDREN

145

TABLE 6. LESIONS OF SKIN, MOUTH AND EYE. VITAMIN A CASES AND CONTROLS COMPARED: SUBDIVIDED BY SEASON.

No. of child-months	Winter 1930-31.		Summer 1931.		Winter 1931-32.		Summer 1932.	
	A cases	Controls						
23·6	36·4	126·4	114·4	225·6	199·5	100·0	125·7	
Lesion.	Per 100 child-months.							
Skin, 'Infective', Napkin rashes, intertrigo, etc.	6·0	4	11·0	7	5·5	10	8·7	4
Dribbling rash	0	—	2·7	0	—	0·9	0	0·8
Balls or whitlow	0	—	13·7	0	6·3	12·2	0	1·6
Eczema	0	—	0	1	0·8	3	1	—
Ringworm	0	—	0	0	—	0	0	—
'Non-infective', Sweat rash or erythema	0	—	0	—	0	5·2	1	9·2
Rough face	0	3·0	0	2·7	7·1	0	1·8	0·8
Urticaria	1	3·0	1	2·7	8	6·3	2	14·3
Anus and urethral orifice.	—	—	—	—	—	—	—	—
Anal tissue or sore at urethral orifice	0	—	0	—	1	0·8	3	1·3
Mouth.	—	—	0	—	0	—	2	—
Ulcer of palate	0	—	0	—	0	—	1·0	1
Thrush or other stomatitis	4	11·9	1	2·7	8	6·3	4	3·0
Cracked lip	0	—	0	—	1	0·8	1	0·5
Eyes.	—	—	—	—	—	—	—	—
Conjunctivitis	3	8·9	0	—	1	0·9	6	2·5
Stye	0	—	0	—	0	—	2·1	—
Blepharitis	0	—	0	—	0	—	0	—

TABLE 7. LESIONS OF SKIN, MOUTH AND EYE. NUMBER OF BABIES AFFECTED IN VITAMIN A GROUP AND IN CONTROLS COMPARED.

No. of infants.	Vitamin A cases.			Controls.	
				60	58	
	Lesion.			No. of infants affected.			No. of infants affected.	
Skin.								
‘Infective.’ Napkin rash, intertrigo, external otitis, septic spots, etc.			15			24		
Dribbling rash	1	16 = 27 per cent.	4	30 = 52 per cent.	
Boils or whitlow	1		3		
Eczema	1		2		
Ringworm	0		1		
‘Non-infective.’ Sweat rash or erythema			4	22 = 39 per cent.	7	5	24 = 41 per cent.	
Rough face					
Urticaria			19		
Anus and urethral orifice.								
Anal fissure or sore at urethral orifice	...		4	= 7 per cent.		3	= 5 per cent.	
Mouth.								
Ulcer of palate	1	19 = 32 per cent.	63	3	57 per cent
Thrush or other stomatitis	17		8	12	
Cracked lip	2		2		
Eyes.								
Conjunctivitis	11	12 = 20 per cent.	8	8 = 14 per cent.	
Stye	3		0		
Blepharitis	0		1		

Since one infant might suffer from more than one lesion (e.g., a napkin rash and a dribbling rash) the figures following the bracket is usually less than the sum of the bracketed figures.

apparent in each subdivision for the different types of lesions, though figures are admittedly small in these subdivisions.

TEXTURE AND MOISTURE OF SKIN AND MUCOUS MEMBRANES. No difference was noted in the texture of the skin or in the degree of moisture of skin or mucous membranes in the two groups. The 'rough face' recorded appeared usually to be an effect of weather or of the soap used. Thus susceptibility to skin infections preceded any obvious clinical changes in the skin, such as have been frequently reported as present before the appearance of xerophthalmia. Nor was any dryness or desquamation discovered in other epithelial structures. At the end of the period of observation the quantity of epithelial cells in the urine of a group of controls and a group of A cases was roughly compared. The number of cells showed very wide variations from individual to individual in both groups, but the average for controls was actually slightly higher than that for A cases.

Discussion of results.

Xerophthalmia and keratomalacia are rare diseases in this country. Yet if it be granted that the evidence here provided proves that the control infants (or a proportion of them), chosen at random from hospital out-patients, and fed in accordance with the author's ordinary hospital teaching (except for the omission of a cod-liver oil supplement) suffered from a slight deficiency of vitamin A, resulting in diminished resistance to infective skin lesions, this slight deficiency must be far from rare among babies not given cod-liver oil, or some other vitamin A supplement. Until working out the data the writer did not realize that the two groups under consideration showed this difference in susceptibility to skin infections. Yet a study of the published clinical accounts of xerophthalmia from this angle brings out forcibly the fact that references to skin changes and infections are very common in any general account of the disease where the attention is not focussed almost exclusively on the eye changes. In rat's eyes slight infection, as evidenced by puffiness of the lids and slight discharge, is apparently usually the first eye change noted¹³. Obvious xerosis appears later, though presumably it is the microscopic epithelial change which has allowed the infection to supervene. It would, therefore, appear that the control children suffered from a degree of vitamin A deficiency which so affected the microscopic structure of their skin as to render it more susceptible to infection, although changes in the skin texture were not apparent on clinical examination. If these babies suffered from vitamin A deficiency, then in view of the apparent rarity in this country at the present time of xerophthalmia in children, one must conclude that xerophthalmia indicates a fairly gross deficiency of vitamin A. Clinical accounts of the disease show that dryness of the skin often precedes dryness of the conjunctiva (Mori¹⁰, Kirkpatrick⁵, Pillat¹¹, Frazier and Hu⁴), so that our cases presumably suffered an even slighter degree of deficiency than would cause obvious dryness of the skin. If the grade of vitamin A deficiency among the controls was so very slight, then the A cases must

have received a large excess of vitamin A. This large excess did not increase the general resistance to catarrhal or other infections.

The question will naturally be asked: Are the babies under consideration representative, or were they receiving less vitamin A than is usual in this country? The babies came from a poor working class district and it is very probable that they were born with smaller vitamin A reserves than babies of parents in good social circumstances. As compared with babies given cod-liver oil, and hence a liberal supplement of vitamin A, our controls were getting much less vitamin A. But there is a tendency nowadays to replace cod-liver oil by other anti-rachitic agents containing no vitamin A, and babies given these are likely to be almost entirely dependent on milk for their vitamin A until they start solid food.

The babies under observation were fed on milk dried by the roller process, and it is the writer's impression that in London more infants are given roller-process dried milk than any other form of artificial food, though, of course, this does not apply to the whole of England, nor to Scotland. The milk used was mostly prepared at intervals of 2 to 3 weeks and was nearly always well under 6 weeks old when consumed, so that if keeping causes slow deterioration of the vitamin A value it compared very favourably with dried milk bought in the open market, which may be months old.

If we consider other forms of milk used in infant feeding we must bear in mind two points: (1) the vitamin A value of the milk itself, and (2) the proportion of the total energy needs supplied in milk and in vitamin A-free carbohydrates respectively. It appears that spray-process dried milk is likely to suffer a greater destruction of vitamin A than roller-process milk, and presumably condensed milk still more so. Some of the infants with xerophthalmia whose histories are recorded in the literature are said to have been fed on condensed milk, though the quantity is not stated (Thalberg¹⁵, Wilson and Dubois¹⁶, Ross¹²). If so-called 'humanized' dried milks, sweetened condensed milks or proprietary foods with dried milk as a basis are employed, the vitamin A content of the diet is likely to be considerably lower than that of our control babies, because a considerable proportion of the total calorie needs of the infants would be supplied in carbohydrate.

It is known that the natural vitamin A content of milk, both of human milk⁹ and of cow's milk⁷ shows wide individual variations, depending largely on the diet. Macy and Outhouse found that the vitamin A content of the pooled milk of 12 wet nurses with healthy babies, and that of the pooled milk of a herd of Holstein cows was about the same. But if the mother's diet is sufficiently deficient in vitamin A, even a breast-fed baby may develop xerophthalmia (Thalberg¹⁵, Mori¹⁰) so the possibility of minor grades of vitamin A deficiency occurring in breast-fed infants of impoverished mothers in this country cannot be excluded, though there is no evidence to prove that it occurs. Possibly an investigation of skin infections in breast-fed babies in a poor district might provide evidence on this point.

What of babies fed on fluid cow's milk? As already stated, the figures of Sherman and Smith would suggest no great destruction of vitamin A in

the process of drying, but further information on this point seems to be needed. If we suppose that some of the vitamin A is destroyed by drying, it does not follow that the baby given fluid milk will get more vitamin A in his feeds, for since fresh cow's milk is less easily tolerated than dried milk, the tendency when giving fluid milk is to supply a larger proportion of the calorie requirements of the babies in vitamin A-free carbohydrate and a smaller proportion in milk.

If we consider the diet after 7 to 8 months old, there is no doubt that the controls received a more liberal amount of vitamin A than do great numbers of our child population. The milk allowance was fairly liberal and the diet was mixed, instead of being heavily overloaded with carbohydrate as happens so often, especially among the poor.

If confirmation of the results recorded in this paper is forthcoming, it would seem reasonable to conclude that slight vitamin A deficiency is widespread, and that a greater deficiency than that shown by the control series in this observation is probably not uncommon.*

With the recognition of the need of systematic anti-rachitic prophylaxis, cod-liver oil has been used on a vast scale in many different countries during the last 12 to 13 years with the excellent result that rickets is becoming a comparatively uncommon disease in many areas. During the last few years with the introduction of irradiated ergosterol, highly potent preparations of vitamin D are tending to displace cod-liver oil, which supplies both D and A, and in this there seems a possible danger unless other means are taken to supply extra vitamin A.

Extra vitamin A can be supplied incorporated in dried milk, as was done in this investigation, and this has the advantage of promoting more regular administration in the case of the less careful mothers. At the present time this would be a somewhat expensive procedure, because the original cost of the vitamin A extract is comparatively high, and because of the amount destroyed in drying the milk. Dr. F. H. Carr estimated that the emulsion of vitamin A derived from mammalian liver added to each pound of dried milk was equivalent to 196 c.c. of cod-liver oil of 7.5 blue value, whereas the quantity present after drying was, by his estimate, equivalent to 67-100 c.c., and by Dr. Coward's estimate equivalent to approximately 30 gm. of cod-liver oil of 12.0 blue value. It has been suggested that the natural vitamin A of the milk is in some way better protected and will withstand procedures which cause a large amount of destruction in added vitamin A.

There is considerable uncertainty as to what is an adequate dose of vitamin D, in the form of irradiated ergosterol, for use in the prophylaxis

* In August, 1933, shortly after these papers had been submitted to the Medical Research Council, Hess, Lewis, and Barenberg, published in the United States the result of a somewhat similar investigation carried out in a home for babies. They concluded there was no evidence of vitamin A deficiency in their control group of infants who received the usual diet of the institution with no supplement of cod-liver oil or vitamin A concentrate, nor did they find any evidence of increased susceptibility to infections of the skin. (*J. Am. Med. Ass.*, 1933, CI, 657.)

of rickets in children, because it appears that there are unexplained discrepancies between the vitamin D value, as calculated from rat experiments, and the requirements of different species of animals. Hence for large scale routine use as a prophylactic for rickets a standardized cod-liver oil appears preferable to irradiated ergosterol in the present state of knowledge. When to this we add the fact that cod-liver oil also provides vitamin A and apparently provides it more cheaply than any of the potent preparations now on the market, it seems that for routine clinical use the profession would do well to stick to cod-liver oil or other standardized fish oils, until such time as a cheaper and better substitute is readily available. A good standardized cod-liver oil can be bought by a hospital at 185 shillings for 25 gallons. Thus 7 pence is the wholesale price of sufficient cod-liver oil to supply a baby with $\frac{3}{4}$ drachm daily for six months, a quantity sufficient to protect him from rickets and, presumably, to provide him also with an adequate supplement of vitamin A.

Summary.

Nature of investigation.—Evidence was sought concerning the existence of a possible vitamin A deficiency in the diet of London babies getting a liberal allowance of milk, and later 'table food' in addition, and on the effect on the health of babies should such a deficiency exist. Between January, 1931, and October, 1932, a period of 22 months, two groups of artificially-fed babies were kept under observation in the out-patient department of the Queen's Hospital for Children. The average period of attendance was approximately 8 months. All were fed on a roller-process dried milk containing iron and ammonium citrate (Hemolac) to which were added vitamin D, orange juice and sugar. From the age of 7 or 8 months, solid food (including eggs, fish, vegetables and meat) replaced part of the milk ration. Approximately half the children (60) received in addition extra vitamin A; the other half (58 children), serving as controls, were dependent for vitamin A on that naturally present in their dried milk or 'table food.' The vitamin A intake of the A cases (though difficult to compute quantitatively, even for the babies entirely bottle-fed, on account of the variations in the estimated vitamin A values of the milk), was, even at the lowest estimate, a number of times as great as that of the controls.

Results.—The addition of vitamin A had no influence on the general health, rate of gain in weight, or on the general resistance to infection, whether to infections of the respiratory or digestive tract or to specific fevers. On the other hand, the incidence of minor 'infective' skin lesions (sore buttocks, intertrigo, etc.), was approximately double in the control group what it was in the A group, and this difference was found to be statistically significant. No difference in the degree of moisture of the skin or in its texture was noted in the two groups. The incidence of urticaria and other non-bacterial skin lesions was approximately the same in the two groups.

The evidence obtained, therefore, strongly suggests that:—

1. Slight vitamin A deficiency existed in our control group, and hence is probably of common occurrence in artificially-fed babies in this country, unless this vitamin is specifically added to their diet by the administration of cod-liver oil or some other potent source of vitamin A.

2. The effect of this slight vitamin A deficiency on the health of infants is to diminish their resistance to infections of the skin such as occur with sore buttocks, intertrigo and dribbling rashes, this susceptibility preceding the obvious clinical changes in the skin texture which have been noted by many observers.

3. Diminished resistance to general infections is not among the first effects of slight vitamin A deficiency in infants, and a large excess of vitamin A does not raise the general resistance.

4. Diminished growth is not among the first effects of vitamin A deficiency in infants.

Further work is desirable to confirm point (2), namely, diminished resistance to skin infections, on which the other conclusions depend, but in view of the uniformity of the results obtained in each season and for each type of skin lesion, it seems most improbable that the difference between the two groups in incidence of infective skin lesions is a matter of chance. No other difference between the two groups was found to be uniform over the seasons. This view is further supported by the high incidence of skin infections and the changes in the skin frequently reported in clinical accounts of xerophthalmia and keratomalacia. These results, if they are confirmed by further work, which the author is undertaking, indicate that artificially-fed babies fed on dried milk, and probably also on fresh dairy milk, require as a routine a vitamin A supplement to their bottle feeds. It is possible that many breast-fed babies of impoverished mothers also require this. It can be supplied, like vitamin D, incorporated in dried milk, but, in the present state of our knowledge, cod- or other fish-liver oil, known to be potent in both vitamins, is probably the most economical supplement for providing the fat-soluble vitamins, and should be used as a routine.

Acknowledgments.—Dr. A. Bradford Hill, of the Medical Research Council's Statistical Department, has very kindly checked the conclusions drawn, thus adding considerably to the value of the work.

Messrs. Cow & Gate Ltd. bore the entire cost of the vitamin emulsions incorporated in the dried milks, as well as the extra expense involved by the preparation of the special milks at short intervals over a period of two years and their chemist, Mr. J. Tavroges, gave his personal supervision to this work and ensured co-ordination of supplies with the work at the hospital. The author recognizes their helpful co-operation with much gratitude.

To Dr. Katharine Coward and Dr. Francis H. Carr, the author is much indebted for their help and kindness in estimating the vitamin A content of the dried milks used. Her thanks are also due to the Medical Officers of Health who co-operated in arranging or the supply of the special milks to necessitous cases,

The work was only possible as a result of the unstinted help and co-operation which was given throughout to the author at the Queen's Hospital for Children. To her colleagues, the nursing staff and others who co-operated she offers her grateful thanks, especially to Miss F. M. Westbrook, Out-Patient Sister—who undertook a large part of the very detailed record keeping, the supervision of the clinics and the distribution of the medicated milk—and to the Dispensing Staff and the members of the Almoner's Office, who very generously undertook much extra work.

In the preparation of these papers the author has received the constant help of Miss Lorel Goodfellow, to whom her sincere thanks are tendered.

REFERENCES.

1. Barnes, J., Brady, M. J., & James, E. M., *Am. J. Dis. Child.*, Chicago, 1930, XXXIX, 45.
2. Catheart, E. P., Murray, A. M. T., & Shanks, M., *Med. Res. Council, Spec. Rep. Series*, No. 151, London, 1931.
3. De Sanctis, A. G., & Craig, J. D., *J. Am. Med. Ass.*, Chicago, 1930, XCIV, 1284.
4. Frazier, C. N., & Hu, C. K., *Arch. Int. Med.*, Chicago, 1931, XLVIII, 507.
5. Kirkpatrick, quoted by Wright, R. E., *Brit. J. Ophth.*, London, 1922, VI, 164.
6. Lossouarn, E., *Presse med.*, Paris, 1932, XL., 745.
7. Luce, E. M., *Biochem. J.*, Camb., 1924, XVIII, 716, 1279.
8. Mackay, H. M. M., & Goodfellow, L., *Med. Res. Council, Spec. Rep. Series*, No. 157, London, 1931.
9. Macy, I. G., & Outhouse, J., *Am. J. Dis. Child.*, Chicago, 1929, XXXVII, 379.
10. Mori, M., *Jahrb. f. Kinderh.*, Berlin, 1904, LIX, 175.
11. Pillat, A., *China M. J.*, Shanghai, 1929, XLIII, 907.
12. Ross, S. G., *Am. J. Dis. Child.*, Chicago, 1921, XXII, 232.
13. Sherman, H. C., & Smith, S. L., *The Vitamins*, second edit., New York, 1931, 272, 274.
14. Steenbock, H., & Kletzien, S. W. F., *J. Biol. Chem.*, Baltimore, 1932, XCVII, 249.
15. Thalberg, J., *Arch. f. Augenh.*, Munich, 1883, XII, 315.
16. Wilson, J. R., & Du Bois, R. O., *Am. J. Dis. Child.*, Chicago, 1923, XXVI, 431.

AN EPIDEMIC OF ACUTE ENCEPHALITIS IN YOUNG CHILDREN

BY

AGNES R. MACGREGOR, M.B., F.R.C.P.E.,

AND

W. S. CRAIG, B.Sc., M.D., M.R.C.P.E.

(From the Departments of Pathology and Child Life and Health, University of Edinburgh, and the Western General Hospital, Edinburgh.)

This paper is concerned with a small outbreak of illness of an unusual nature occurring in the Children's Unit of the Western General Hospital, Edinburgh. In addition to the clinical interest of the cases, there are features of considerable pathological and epidemiological importance connected with the outbreak.

Clinical Records.

Case 1. I.M.S., female, aged 1 year 7 months, was admitted to the Western General Hospital in March, 1933, at the age of 1 year 3 months. At this time she was noted as being slightly undersized but well nourished and the liver showed moderate enlargement. Prior to admission she had been treated elsewhere for gonococcal vaginitis: during the three succeeding months her health was good and progress uninterrupted, but a positive Wassermann reaction, present on admission, persisted. On the evening of July 22, 1933, the patient was noticed to be less active than usual and generally 'out of sorts': her condition remained unchanged throughout the rest of the day, and on the 23rd she was still quieter and less responsive to all forms of attention and refused food. By the afternoon of the 24th she was definitely dull and apathetic. She lay awake for long periods in her cot but without changing her position or showing response to external stimuli. The expression was heavy and drowsy, the face flushed, the conjunctivae suffused and the eyes dark-ringed and sunken. The tongue was furred and the fauces were injected. Temperature and pulse rate were normal; there was no rash, and examination of the child resulted in only negative findings. At this stage the patient was isolated with three other children (C.B., M.M., E.M.W.) from the same ward who were showing similar but less marked signs in keeping with the prodromal stage of some common infective disease.

At 10.30 p.m. of the same day (July 24) the child's condition became suddenly worse and she looked extremely ill: left undisturbed she lay motionless, staring in front of her without interest, but when examined was excessively fretful. No evidence of organic nervous disease was found. Temperature was still normal. About this time vomiting took place and recurred several times during the night. The motions were loose, but neither foetid nor frequent. There was never any improvement in the child's condition, and at 1.30 a.m. on the morning of July 25

the temperature rose to 103.2° F. This was accompanied by an acceleration of pulse which became increasingly rapid until it was imperceptible. Repeated cerebral cries were noted before the child became comatose and died at 5.30 a.m., sixty hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (12 hours after death).

BRAIN. There was hyperaemia of the meninges at the base, but not elsewhere; no thrombosis of meningeal vessels, nor haemorrhage. The brain substance, both grey and white matter, was markedly congested, especially in the pons. No areas of softening were observed.

FAUCIAL TONSILS were enlarged but not obviously inflamed.

THE LUNGS were congested and there was atelectasis of the left upper lobe.

THE LIVER was slightly enlarged, firm, pale, tough, and showed fine fibrosis.

THE KIDNEYS were healthy.

MICROSCOPIC EXAMINATION. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons and medulla oblongata. All the parts examined showed considerable hyperaemia, which was accentuated in certain areas and was

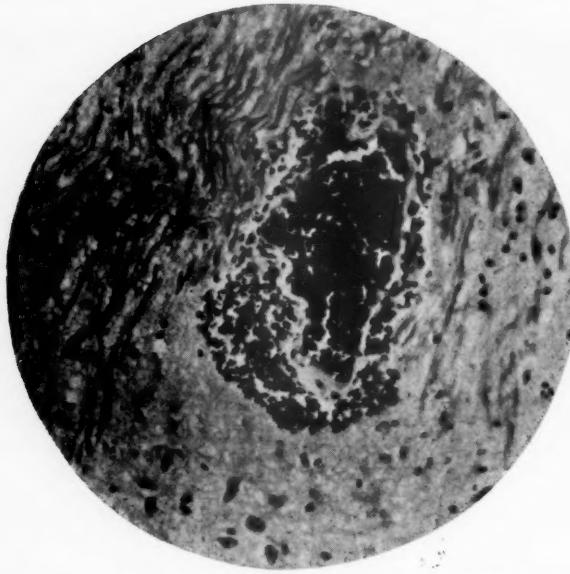


FIG. 1. Blood vessel in optic thalamus showing haemorrhage into perivascular space. (Case 1.)
x 150. H. & E.

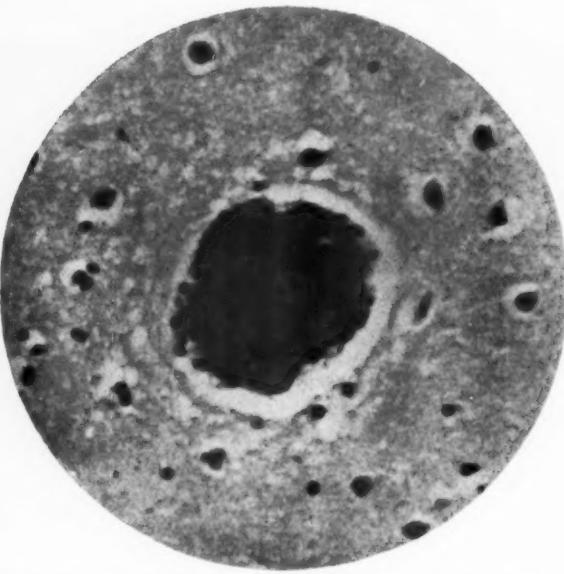


FIG. 2. Venule in optic thalamus, showing early perivascular infiltration. Small mononuclear cells in perivascular space, arranged in a ring around the vessel. (Case 1.)
x 300. H. & E.

generally more severe in the grey matter than in the white. This was particularly noticeable in mid-brain, pons and medulla where the congestion was greatest in the grey matter beneath the floor of the fourth ventricle and around the Sylvian aqueduct. Haemorrhage into the adventitial space of blood vessels was a noteworthy feature, especially in the optic thalamus (Fig. 1). The extravasated blood was, as a rule, strictly confined within the peri-vascular space, but occasionally it had penetrated to a short distance into the surrounding brain substance. There was oedema of the brain, shown by dilatation of the perivascular spaces, and an increase in the size of the spaces surrounding nerve cells. Perivascular infiltrations of small round cells ('cuffing') were not found in typical form, but evidence of commencing infiltration was forthcoming. A venule in the optic thalamus had a ring of small lymphocyte-like cells, one layer thick, lying in the dilated perivascular space, closely applied to the vessel wall (Fig. 2). A few other vessels showed three or four similar cells in the perivascular space.

Changes indicating injury to nerve cells were conspicuous but not extreme. They were best observed in the large ganglion cells in the floor of the fourth ventricle and central grey matter of the mid-brain; also in the larger nerve cells of the thalamus. The changes included swelling of the cell body, the outline becoming convex, chromatolysis with partial or almost complete disappearance of the Nissl substance, an eccentric position of the nucleus, which sometimes bulged beyond the edge of the cell body, and, in a few of the more gravely injured cells, karyolysis, the nucleus staining so faintly as to be almost indistinguishable. These changes were very variable in degree in different cells and those affected were irregularly distributed. In a single group of ganglion cells some might show severe changes while others appeared quite healthy. Occasional nerve cells had three or four satellite cells, but true neuronophagia was not observed. In the pons and medulla many of the large ganglion cells close to the floor of the fourth ventricle contained small strongly eosinophilic granules in their cytoplasm, either aggregated in a clump or dispersed throughout the cell body (Fig. 3). The



FIG. 3. Large nerve cells in floor of fourth ventricle. Each cell contains a cluster of minute eosinophilic bodies in the cytoplasm. The nuclei are eccentric in position. (Case 1.) $\times 600$. H. & E.

cells which contained these granules often exhibited in relatively severe degree the various degenerative changes described above. Such granules were not found in any other part. Intranuclear inclusion bodies were not found.

Sections of lung, spleen, kidney and lymph gland showed nothing of pathological significance. Toxic changes were practically absent. In the liver there was an increase of cellular fibrous tissue, infiltrated by lymphocytes, in the portal tracts, and in a few places this tissue had penetrated the lobules. There was also some fatty change in the liver cells. These changes were attributed to congenital syphilis.

Case 2.—C.B., male, aged 1 year and 7 months. He had no illness during infancy other than measles at eight months and occasional attacks of bronchial catarrh. On April 19, 1933, at the age of 1 year and 4 months, he was admitted to the Western General Hospital as a healthy child. He was discharged to the Edinburgh City Hospital with chickenpox on June 4, being readmitted to the Western General Hospital on June 17 in a robust, healthy condition. On July 24, 1933, he was noted to be less active than usual and to have no desire for food.

By evening his face was flushed, his eyes injected and his expression heavy and dull. The tonsils were enlarged and red, the tonsillar glands moderately swollen. Temperature was normal; there was no rash, but, as a precaution, the child was isolated. Temperature was still normal on July 25. The child's condition was one of great agitation which tended to exhaust him so that he was alternately restless and very listless. On being approached he showed intense irritability, and attempts to examine him were resisted with vicious frenzy; he scratched and tore anything within reach, and flung himself about the cot. Pupils were dilated but equal, there was some diminution in arm tendon reflexes, superficial abdominal reflexes were absent, the left knee jerk was increased, and a right extensor toe response was obtained. A true Kernig's sign was not found, but there was definite objection to attempts to elicit it on the left side. Tâche was pronounced. Curious features were the way in which the child screwed up his eyes whenever a hand was brought near his forehead, and a tendency to assume a position of extreme opisthotonus in his endeavour to resist examination. Examination left him extremely exhausted. No localised muscle tenderness was determined. The tongue was moist but heavily coated. Examination of the chest and abdomen was entirely negative. The tuberculin test was positive. The white blood count was 18,000 per c.mm., consisting of polymorphs 57 per cent. and mononuclears 43 per cent. A specimen of stool examined contained no pathogenic organisms. By midnight on the 25th the child looked extremely ill; his expression was dazed, his eyes sunken and ringed; he was definitely drowsy although still able to resist examination violently. The pulse was now very rapid and soft. Lumbar puncture was carried out, and 60 c.c. of clear fluid obtained under pressure. This appeared to result in a slight improvement, but any benefit was only of a temporary nature. By 9 a.m. on July 26 drowsiness had been replaced by a state of intense irritability and restlessness. The patient flung himself about in his cot until, completely exhausted, he lay curled up, his head buried in the pillow. He uttered frequent piercing cries and was obviously in great pain: the lips were ashen, the conjunctivæ markedly injected, the right more so than the left, and the pulse continued to become increasingly rapid. Lumbar puncture was again carried out and 10 c.c. of clear fluid obtained under pressure.

At 10 a.m. the child was again examined. Both pupils were contracted, the left more than the right. The eyes were turned upwards and towards the left and blinking was abolished on the left side. A dubious Kernig's sign was elicited on both sides but there was no neck rigidity. The patient continued to utter periodic cries of pain, but these became weaker: he lay continually on his right side, passed into a semi-comatose condition, and died at 12.20 p.m., forty-eight hours from the time of onset of the illness.

POST-MORTEM EXAMINATION (24 hours after death).

BRAIN. There was intense hyperaemia of the meninges over the whole surface; no thrombosis of blood vessels. The brain substance showed intense congestion of both grey and white matter; the grey matter had a pinkish colour and congested vessels were prominent in the white matter. No haemorrhages or areas of softening were visible.

SPINAL CORD showed congestion of the meninges.

FAUCIAL TONSILS were enlarged.

TRACHEO-BRONCHIAL LYMPH GLANDS: one contained a few small tuberculous foci.

LIVER AND KIDNEYS showed very slight toxic changes. No other organ presented anything abnormal.

MICROSCOPIC EXAMINATION. Sections were examined from cerebral cortex, optic thalamus, mid-brain, pons, medulla oblongata and spinal cord. Intense congestion of the brain substance was present in all the parts examined. The adventitial spaces of blood vessels were distended and the pericellular spaces increased in size, indicating oedema of the brain. Haemorrhages into perivascular spaces were numerous in the optic thalamus and present also in pons, medulla and mid-brain; they were not found in cerebral cortex or spinal cord. Typical 'cuffing' of blood vessels with infiltrations of small round cells could not be demonstrated,

but in the dilated perivascular spaces of a few blood vessels in the mid-brain small collections of mononuclear cells were found (Fig. 4). The best examples were in the central grey matter near the aqueduct, and in the region of the substantia nigra. In other parts of the brain and in the spinal cord no such appearance was discovered.

Ganglion cells presented variable appearances. Many showed no alteration. Others were profoundly altered, being swollen, showing chromatolysis of varying degree, and having the nucleus displaced to one side of the cell. Sections stained to demonstrate Nissl bodies (cresyl violet) showed in many cells the condition of central chromatolysis, the Nissl substance having disappeared from the central part of the cell body and being collected in a dense mass or ring at the periphery (Fig. 5). The nucleus of such cells might be healthy, but was usually eccentric in position and sometimes showed karyolysis. These changes in nerve cells were more pronounced in the central grey matter and substantia nigra of the mid-brain than elsewhere, but were found in certain cells in the thalamus, pons and medulla. They were not observed in the cerebral cortex nor

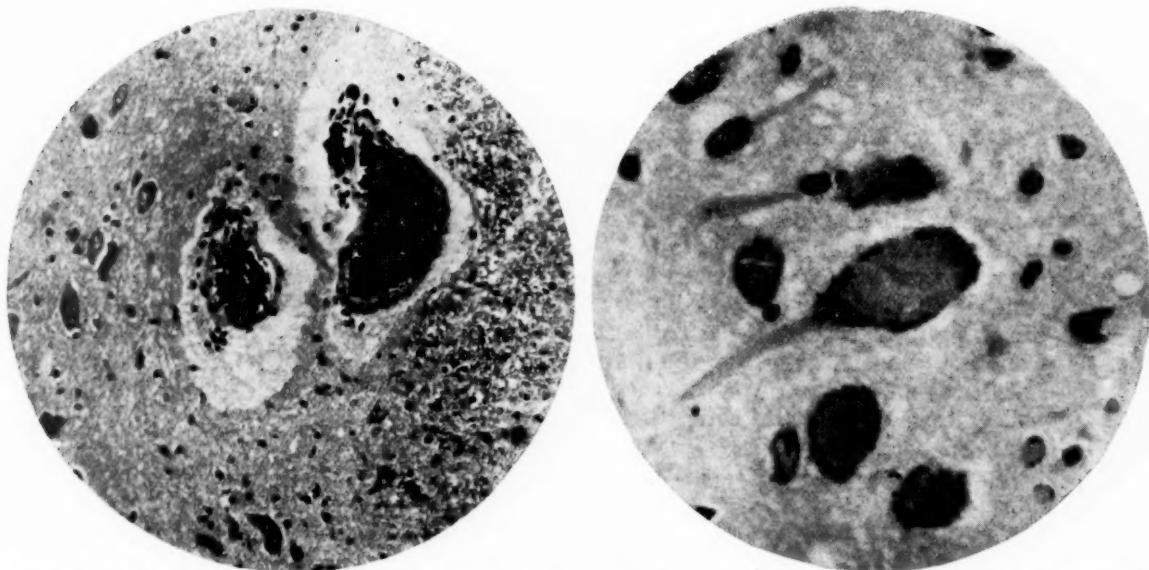


FIG. 4. Small blood vessels in central grey matter of midbrain. The perivascular spaces are widely dilated and in them a few small mononuclear cells have collected. (Case 2) $\times 150$. H. & E.

FIG. 5. Degenerate nerve cell in central grey matter of midbrain, showing disappearance of Nissl substance from central part of cell body (central chromatolysis). (Case 2) $\times 580$. Cresyl Violet.

in the cord. No inclusion bodies, either intranuclear or extranuclear were found.

Sections stained by Morgan's method for myelin showed no areas of demyelination.

Sections of liver, spleen and kidney showed no significant changes. Toxic degeneration was very little in evidence. Sections of lung showed nothing except some general hyperaemia.

Case 3.—M.M., female, aged 1 year and 11 months.

Born in the Maternity Ward of the Western General Hospital in August, 1931, she remained in the Hospital until she contracted chickenpox in March, 1933, at the age of 1 year and 7 months. She was readmitted in good health from the City Fever Hospital on May 13, following the attack of chickenpox.

On the morning of July 23, 1933, she was noticed to be less active than usual and without desire for food. Her condition was much the same the next day but her face was flushed and her expression heavy. Temperature was normal, and nothing was found on examination beyond moderate enlargement of the

tonsils and faecal injection. As a precaution the child was removed to the isolation ward.

Complete examination was again carried out on the afternoon of July 25. An extensor plantar response was obtained on the left side; otherwise the superficial and tendon reflexes were normal. The ear drums were healthy in appearance; the urine contained nothing abnormal. The one noticeable change from the previous day was increasing restlessness and irritability. By the afternoon of July 26 this irritability was extreme and made examination difficult. Kernig's sign was not present but the patient resented extension of the legs although there was no apparent muscle tenderness. Superficial abdominal reflexes and the biceps tendon jerks were absent. Sweating of the head was a feature and there was a pronounced tâche. A specimen of stools contained no pathogenic organisms. The tuberculin skin test was negative. Towards evening the restlessness was further increased, and lumbar puncture was carried out, 10 c.c. of clear fluid being obtained under slight pressure with resultant relief.

The next day, July 27, the patient's objection to examination was greater. She flung her head back, rigidly arched her spine, uttered piercing cries and tore at anything within her reach. She appeared in terror of having her head touched and screwed her eyes up in a characteristic way when this was attempted. The pupils were widely dilated and there were dark rings around the eyes. Abdominal and tendon reflexes remained unchanged from the previous day. Examination left the patient extremely exhausted. She occasionally sat up and took an interest in her surroundings but soon relapsed into her former drowsy state. A white blood count gave 12,000 cells per c.m.m. of which 60 per cent. were polymorphonuclear and 40 per cent. mononuclear.

The next morning, July 28, the child's general condition showed slight improvement and at times she was seen to smile, but still showed the same maniacal frenzy when any attempt was made to examine her. When undisturbed she was still abnormally quiet and unresponsive. Tendon reflexes were unchanged from the previous day. For the first time there was limitation of neck flexion. Lumbar puncture was carried out and 30 c.c. of clear cerebro-spinal fluid obtained under pressure, after which the restlessness was greatly diminished. A few hours later the child was transferred to the City Hospital. The abdominal reflexes reappeared two days after transfer and the pulse rate remained accelerated for almost two weeks. Otherwise there was nothing to note, and recovery was apparently complete. At the present time her condition is excellent and she shows no residual manifestations of her illness.

Case 4.—E.M.W., female, aged 2 years. The child was first admitted to the Western General Hospital in July, 1932, at the age of one year after a severe attack of measles. No other details of the previous history were available. At the time of admission her condition was poor: this improved greatly during the twelve months she was in hospital, despite the fact that she was subject to recurrent attacks of respiratory and alimentary catarrh. The tuberculin reaction was positive.

On the morning of July 24, 1933, she was noticed to be off colour, apathetic and refusing food. By the afternoon her expression had become heavy, the face flushed and the eyes suffused. Usually of a distinctly friendly nature, she was now very peevish. Temperature was normal. There was an occasional short dry cough. Tonsillar glands were palpable; the tonsils were slightly enlarged and injected. Otherwise the findings on examination were negative. Her condition remained unchanged throughout the next day, but by the afternoon of July 26 her lassitude had greatly increased. During examination irritability was extreme; she flung her head back and assumed the position of marked opisthotonus and uttered repeated shrill cries. Absence of the abdominal reflexes and diminution of the biceps and supinator reflexes were noted and there was a pronounced tâche cerebrale. There was no nuchal rigidity, Kernig's sign was absent, and there was no ocular paresis. The tongue was furred, and the motions were green and increased in frequency but contained no pathogenic organisms. The urine was

normal. A white blood count was 15,200 per c.mm. and a differential count gave polymorphonuclears 65 per cent. and mononuclears 35 per cent.

On the afternoon of the next day, July 27, Babinski's sign was obtained on the right side, while the response on the other side was dubiously extensor. Nuchal rigidity and Kernig's sign were absent but marked voluntary resistance was encountered in testing for these. The abdominal reflexes were still absent, the pupils were now widely dilated, and the expression one of fear. The child was terrified when a hand was brought near her head. Irritability was still extreme and examination left her greatly exhausted. There was no evidence of localised muscle tenderness. The pulse was rapid.

During the night the child became more restless and walked round her cot until, tired out, she lay down. Early in the morning (July 28) she vomited. Examined again at 10 a.m. she resisted with a maniacal frenzy until exhausted. The abdominal reflexes were absent, Babinski's sign was obtained on both sides, and Kernig's sign was found on the right side but not on the left. Vomiting occurred twice during the course of the morning. Lumbar puncture was performed and 30 c.c. of clear fluid obtained under pressure, giving immediate great relief. Three hours later the patient was transferred to the City Hospital. There her progress was uninterrupted; doubtful neck rigidity persisted for a further forty-eight hours and the pulse, which had become rapid while she was still in the Western General Hospital, did not return to normal until ten days after transfer. The abdominal reflexes reappeared two days after admission to the City Hospital. At the present time the child is in excellent health and shows no evidence of any sequelae.

SUMMARY OF PATHOLOGICAL INVESTIGATIONS

Case number.	Initials.	Date.	C.S.F. Mgms. per 100 c.c.			Blood.			W.R.	T.R.
			Protein.	Sugars.	Chlorides.	W.B.C. per c.mm.	Polymorpho-nuclears. %	Mononuclears. %		
1	I.M.S.	January, 1933 25/7/33	... Blood stained	... stained	... stained	+	
2	C.B.	January, 1933 25/7/33 26/7/33	... 20	... 80	... 737	... 18,000	57 43		+
3	M.M.	13/7/33 26/7/33 27/7/33 28/7/33	... 60 ... 61	... 25 ... 87	... 735 ... 584	... 12,000	60 40		
4	E.M.W.	August, 1932 26/7/33 28/7/33 22 99 528	15,200	65 35		+

C.S.F. All cases { Cells all lymphocytes, no increase.
Culture sterile; colloidal gold reaction, no precipitate.
(Specimen from Case 1 taken at autopsy).

BLOOD. Cultures made of heart blood at the autopsies on Case 1 and 2, both sterile.

FAECES. All cases; no pathogenic organisms isolated.

URINE. All cases; no microscopical abnormalities.

Clinical summary.

All four children had been in hospital for a prolonged period; two for over three months and two for twelve months. They were all admitted as healthy individuals on the recommendation of the Public Assistance Officer. Three (I.M.S., C.B., and M.M.) were in the same ward, the first two occupying adjacent cots. The fourth child was in a different ward, but was attended by the nurses in charge of the other three cases. Between July 7 and July 11, when the heat was exceptionally great, the four children, along with other inmates of their wards, spent the greater part of each day in the garden adjoining the hospital. Among adult female patients also in the garden were two cases of post-encephalitic Parkinsonism who found a special delight in the companionship of the children. The children I.S. and C.B. were especial favourites and were known to have played for long periods on the knees of one or other of these particular patients. The third child (E.M.W.) was known to have been in similar contact on occasions with the post-encephalitic subjects, but any history of such contact in connection with the fourth child (M.M.) was vague.

The four children fell ill within a period of 36 to 48 hours. The clinical picture presented as the disease ran its course was very similar in all four cases. After an insidious onset extending over a period of some thirty-six hours, characterised by catarrh, lethargy and heaviness of expression, the children became distinctly drowsy but at the same time resisted examination with an almost maniacal frenzy. Nothing abnormal was found on examination of the nervous system five hours prior to death in the first fatal case (I.S.), but in each of the remaining cases Babinski's sign was obtained and the superficial abdominal reflexes were absent. Ready exhaustion, a fear of having the head touched and a pronounced tâche were other constant features. The two surviving patients were afebrile throughout, and in the two fatal cases the temperature only rose during the terminal phase, and in one instance (C.B.) this was preceded by an increase in the respiratory rate. In both fatal cases cerebral cries were noted. Vomiting occurred in two patients. Ophthalmoplegia was seen in only one (C.B.), and then only an hour before death. Kernig's sign and neck rigidity, when they occurred, were rather indefinite and showed a tendency to vary from hour to hour. There were no convulsions and no myoclonic movements. The condition of the two children who died became critical with great suddenness; in those who recovered, the improvement following lumbar puncture was dramatic. The three blood examinations carried out all showed a slight relative polymorphonuclear leucocytosis. The cerebro-spinal fluids taken during the stage of active disease all showed a slight increase in the sugar content and a reduction in the chlorides, unaccompanied by any appreciable increase in cell content. Protein in one surviving case was very slightly increased.

Pathological summary.

The outstanding pathological findings in both cases were remarkably similar. Both showed intense congestion of meninges and brain substance, especially the grey matter, oedema of the brain, perivascular haemorrhages, and degenerative changes in nerve cells. Typical cuffing of blood vessels could not be demonstrated, but evidence of the earliest stage of perivascular infiltration was found in the form of collections of a few small mononuclear cells in the adventitial spaces of certain blood vessels. Perivascular demyelination had not occurred.

Caution is necessary in accepting the changes in nerve cells as a genuine effect of disease. Such alterations are admittedly capable of being produced by post-mortem autolysis or by imperfect fixation. The very unequal incidence of the changes in different cells, however, argues in favour of true ante-mortem degeneration. It was remarkable how, in a single small group, certain cells might be profoundly affected and others, close by, present a perfectly healthy appearance. Such a selective effect, while recognized as a common occurrence in true degeneration, is very unlikely in the case of any factor operating after death.

The minute eosinophilic granules observed in the cytoplasm of certain nerve cells in the floor of the fourth ventricle in case 1 were probably merely products of cell degeneration. They do not appear to be of the same nature as the extranuclear granules described by da Fano and others⁶.

The distribution of the lesions is important. This was similar in the two cases. Congestion and oedema were general throughout the brain, but the graver lesions were found only at the lower levels. Perivascular haemorrhages and nerve cell changes were best seen in the thalamus, mid-brain, pons and medulla; they were not found in the cerebral cortex. The early infiltrations were discovered only in the region of the substantia nigra and central grey matter of the mid-brain in one case, and in the thalamus in the other. The spinal cord, in the one case in which it was examined, showed only a degree of congestion.

Attempts to obtain experimental infection in animals by inoculation of cerebro-spinal fluids from cases 1 and 2 were made by Dr. J. M. Alston, who reported as follows:—

CASE 1. Cerebro-spinal fluid was injected intra-cerebrally into two rabbits, two guinea-pigs and six mice. No result was obtained except that one rabbit died seven days after injection. Intra-cerebral injection of two more rabbits from the brain of this animal produced no results.

CASE 2. Intra-cerebral injection of cerebro-spinal fluid into two rabbits, two guinea-pigs and four mice was followed by no result except that one rabbit showed nervous symptoms three days after injection and was killed. Two rabbits injected intra-cerebrally with filtrate of this animal's brain showed no ill effects.

Discussion.

The epidemic nature of the condition is indicated by the almost simultaneous appearance of the initial symptoms, and the occurrence of

all four cases in a single nursing unit. A remarkable feature of the epidemic was the rapidly fatal course of two cases.

Differential diagnosis.—On both clinical and pathological grounds the cases may be regarded as a type of acute encephalitis. Clinically this was suggested by the alternation of marked drowsiness and intense restlessness, amounting at times to frenzy; these occurring in the absence of evidence of meningeal irritation such as nuchal rigidity and Kernig's sign. Ophthalmoplegia occurred in one case; vomiting and cerebral cry were noted in two. Further evidence of organic changes in the central nervous system was afforded by extensor Babinski responses and loss of abdominal reflexes. Changes in other reflexes were variable. The sudden unexpected death in the first case, at a time when other children were showing lethargy and irritability, suggested that the condition might be encephalitis of an epidemic nature. The results of the autopsies on the two fatal cases supported this diagnosis; no significant pathological changes were found anywhere except in the brain, and meningitis was not present.

The absence of a pathological picture completely characteristic of any particular type of encephalitis leaves the question of more exact diagnosis open to discussion, and various possibilities have to be considered.

1. Food poisoning and alimentary infections.—The fact that among the fifty-one children in the wards from which the cases were drawn no others were similarly affected although all received food from the same source, virtually rules out the possibility of botulism or other form of food poisoning. In all four cases examination of the stools for pathogenic organisms proved negative.

2. Heat and sunstroke.—The epidemic occurred at a time of exceptionally hot weather when all the children in the wards spent the greater part of each day out of doors. They were provided with sun-bonnets and kept in the shade. Neither clinical nor pathological facts support a diagnosis of heat or sunstroke.

3. Acute toxic encephalitis has been described occurring as an accompaniment of severe infections^{10, 15}. The possibility of there being any hidden focus of infection in our cases was ruled out by the afebrile course, the results of blood examination, and the failure to discover any source of toxæmia either clinically, or at autopsy on the two fatal cases. Further, the histological changes did not correspond to those described in acute toxic encephalitis by various observers.

Brain, Hunter and Turnbull² described six cases of acute meningo-encephalo-myelitis which they attributed to 'some unknown toxæmia,' without evidence of infection. Clinically, these cases resembled ours in certain particulars, but differed notably in the constancy of evidence

of meningeal involvement and in the presence of fever in five of the six cases. On pathological examination the one fatal case showed congestion, oedema, perivascular haemorrhages and nerve cell changes similar to those found in our cases, though more widely distributed; it differed in the complete absence of any evidence of perivascular infiltration. A further point of difference was the presence of very advanced degenerative changes in the liver and kidneys. The one abortive case in this series (case 3) bears a close resemblance to our two recovered cases, particularly in the rapid improvement following lumbar puncture. This case differed from the others in several important particulars, and it seems to us by no means certain that it was of the same nature.

4. Varicella encephalitis.—Two of the children had had an attack of varicella earlier in the year, and had been readmitted from the City Fever Hospital as non-infective, the one ten weeks and the other five weeks before the onset of the illness. The usual interval between the onset of varicella and the appearance of complications involving the nervous system is about nine or ten days²⁹; Winnicott and Gibbs³², reviewing the literature, state that the extremes are four to thirteen days. It is unlikely, therefore, that varicella had any connection with the condition in these two children, and this is further borne out by the fact that, according to Winnicott and Gibbs, no fatal cases of varicella encephalitis have been reported.

5. Vaccinia.—None of the four patients, none of the other children in the wards, and none of their attendants had been vaccinated during the year.

6. Acute disseminated encephalo-myelitis.—Boyd¹ describes under this title a form of encephalitis quite distinct from the lethargic encephalitis of von Economo. He includes in this category post-vaccinal and post-infectious encephalitis and also a spontaneous type, which forms much the largest group. The clinical picture of this condition, as described by Boyd, shows little resemblance to that observed in our cases. According to him, the essential histological lesion is the presence of areas of perivascular demyelination scattered widely throughout the brain and spinal cord. Nothing at all resembling this was found in our cases.

7. Other epidemic forms of encephalitis.—

A. 'TYPE B-ENCEPHALITIS' AND 'X-DISEASE.'—Type B-encephalitis has occurred in epidemic form in Japan on many occasions during the last sixty years³³. X-disease was met with in Australia in 1913 and 1918^{33, 4, 29}. Pathologically these conditions show many features in common with the encephalitis lethargica of von Economo, but at the present time authorities are still inclined to regard them as separate diseases³³. Clinically they closely resemble each other. They appear to be virus infections of the central nervous system tending to occur during

exceptionally hot weather, but otherwise the clinical picture they present does not resemble that of our cases.

B. THE EPIDEMIC IN ST. LOUIS, U.S.A. (1933).—This has been regarded as a type of encephalitis distinct from the lethargic form¹. The distinction is based upon both clinical and pathological grounds. Paresis when it occurred was only transient, ocular palsies were notably absent, and, so far as can as yet be ascertained, there were no sequelae. The pathological lesions occurred at higher levels, without special localisation in the mid-brain or basal ganglia¹¹, and cellular infiltrations occurred with no relation to vessels¹⁶. Although our cases resembled this type in the initial catarrhal phenomena and in certain features during the later stages, they differed markedly in the absence of fever, the occurrence of ophthalmoplegia and the distinct localisation of the graver pathological changes, including early infiltration, in the bulbar region and basal ganglia.

C. ACUTE SEROUS ENCEPHALITIS.—Under this name Brown and Symmers³ described ten cases which resembled ours in both clinical and pathological features. Their cases all occurred in children during the summer, ran a rapidly fatal course, and showed catarrhal phenomena and signs of general nervous involvement. They differed from our cases in their febrile nature, in the occurrence of convulsions and in the presence of other localising signs. The pathological data set forth in their paper are scanty, but the changes described, including engorgement of blood vessels of the brain, oedema, perivascular haemorrhages and focal collections of cells, resemble those found in our cases. There is no reference to the exact distribution of these lesions. It is doubtful whether the cases described by Brown and Symmers represent, as they claim, a separate entity.

D. POLIO-ENCEPHALITIS.—In the literature there is general agreement that differentiation between the encephalitic form of polio-myelitis and epidemic encephalitis is uncertain. It has even been suggested that cases hitherto regarded as of the former type should rather be classed as epidemic encephalitis¹³. This view is supported by the fact that the virus of polio-myelitis has not been isolated from a case in which the clinical diagnosis of polio-encephalitis has been made¹³.

The fact that polio-myelitis was not prevalent in epidemic form in the district at the time is in itself an argument against regarding our cases as examples of that disease. The absence of fever, the nature of the changes in the reflexes and the predominance of females among the patients are all facts contrary to those usually associated with polio-myelitis. Another important argument is the bizarre character^{34, 12} of the clinical picture and the lack of evidence pointing to cord lesions.

Pathologically there appears to be no criterion by which certain distinction can be made in all cases between epidemic encephalitis and the bulbar form of polio-myelitis. In the Report of the International Committee for the Study of Infantile Paralysis¹³ the statement is made

that 'the histological lesions (in poliomyelitis) cannot be differentiated with certainty from those of epidemic encephalitis.' More recently Freeman⁸ also has emphasised the similarity of the lesions in the two conditions. Points against the diagnosis of polio-encephalitis in our cases are the relatively slight damage to the nerve cells, and the absence of lesions in the spinal cord in the one case in which it was examined, and the completely inconclusive results of the attempts to transmit the infection to animals. McIntosh¹⁷ considers that these three points are sufficient to distinguish encephalitis lethargica from cerebral polio-myelitis. Kinnear Wilson³¹ emphasizes the prominence of haemorrhage in encephalitis as a distinguishing feature in differential diagnosis.

E. EPIDEMIC LETHARGIC ENCEPHALITIS.—As our cases resembled this condition in many features it is necessary to consider these in detail.

a. **Epidemic form.** It is recognized that it may occur in the form of limited outbreaks in institutions. McNalty and Hall^{20, 11} have collected a number of reports of such outbreaks in this country, and Duzar and Balo⁵ recorded an institutional epidemic in Budapest.

b. **Season.** Although epidemic encephalitis has its maximum incidence in the colder months, outbreaks have occurred during hot weather²⁰. Hall¹¹ draws attention to the fact that most of the few outbreaks of encephalitis lethargica of a definitely contagious character have occurred at periods of the year when the disease was not present in epidemic form.

c. **Age.** Although encephalitis lethargica is generally regarded as a disease which affects adults more often than children, its occurrence in newborn infants, of which several well authenticated cases have been reported²², proves that even the youngest are not immune. Furthermore McNalty²⁰ reported a fatal case occurring in a child aged one year nine months; Netter²⁵ described a case occurring in an infant of two months; and the eleven cases in the Budapest epidemic were all in infants a few months old.⁵

d. **Predisposition.** Syllaba and Henner²⁰ emphasize the importance of predisposition towards infection. Such predisposition was met with in children of unhealthy parentage and they particularly mention that many patients were children of syphilitic parents. Our four children were all poor-law patients; one was a congenital syphilitic and two gave positive reactions to the tuberculin skin test.

e. **Result.** Our two fatal cases correspond exactly in the matter of age and duration with the case described by McNalty²⁰ in a female child aged one year and nine months who died after two days' illness. The same authority²⁰ has recorded improvement following lumbar puncture similar to that which occurred in our two recovered cases.

f. **Clinical features.** Certain features of the clinical picture already described have been stressed by other observers. Among these are the following :—

Duration of the prodromal period. McNalty¹⁹ states that the prodromal period is commonly one to seven days and that, particularly in children, it tends to be brief. In our case signs of active disease were present within 24 to 36 hours of the appearance of initial signs of illness.

Early catarrhal phenomena. These occurring in relation to the throat, conjunctivae and intestine have been particularly emphasized by McNalty¹⁹, Riley²⁸, Duzar and Balo⁵ and others¹⁸.

Absence of fever. Fever was present only during the terminal stages in the two fatal cases, the other two being afebrile throughout. Kinnear Wilson³¹ and Hall¹¹ remark upon the frequent absence of fever throughout the course of the illness; McNalty¹⁹ considers that afebrile cases do not exist but believes that a rise in temperature may be a late event. Syllaba and Henner³⁰ in a review of a thousand cases encountered a number which ran afebrile courses and concluded that the elevation of temperature paralleled the patient's general condition.

General symptoms and signs. The symptoms in our cases were admittedly vague and the findings noticeably variable. The protean character of epidemic encephalitis is frequently mentioned in the literature^{34, 28, 12} and has been emphasized as an observation of especial value in differential diagnosis¹³. Among the few constant findings in our cases was the absence of abdominal reflexes. Raimist²⁷ and Price²⁶ consider this phenomenon to be of diagnostic importance and emphasize that these reflexes return with recovery. The indefinite way in which the prodromal period merged into the stage of active disease corresponds with what McNalty¹⁹ has described as a typical history of encephalitis lethargica. The alternation of irritability and lethargy, so prominent in our cases, is emphasized by Kinnear Wilson³¹ and others. Ophthalmoplegia, which occurred in one of the cases, is a frequent and important finding in lethargic encephalitis.

g. The blood and cerebro-spinal fluid. In two of three of our cases in which an examination of the blood was carried out there was a slight leucocytosis; in all three there was a small relative increase in the number of polymorphonuclear cells. These findings are in agreement with those of Holt¹² and Riley²⁸ in connection with encephalitis lethargica.

According to McNalty¹⁹ and Wilson³¹ the cerebrospinal fluid shows no characteristic changes in encephalitis lethargica. Boyd¹ is in agreement with these authorities but states that the fluid may show a moderate lymphocytosis. Holt¹² maintains that the fluid may be normal during the acute stage but commonly shows an excess of mononuclear cells at a later period. Syllaba and Henner³⁰ and Riley²⁸ consider that sugar is often present in excess. The changes present in the fluids obtained from our patients (see table) were in keeping with those recognized by these observers as occurring in epidemic encephalitis lethargica.

h. Pathological features. In certain respects the pathological changes resemble those of encephalitis lethargica:—

The distribution of the lesions. There is general agreement among observers that while congestion and oedema may be universal throughout the brain in encephalitis lethargica, the perivascular lesions and nerve cell changes have a characteristic distribution. The parts most affected are the region of the substantia nigra and central grey matter of the mid-brain, the pons and medulla oblongata, and the basal ganglia, especially the optic thalamus; the cerebral cortex is spared and the spinal cord little involved. This distribution is claimed by McIntosh¹⁷ as one of the most striking features of the lesions. The same fact is emphasized by Zinsser³⁴ and Freeman⁸. This characteristic distribution of the graver pathological changes was found in both our fatal cases.

The nature of the pathological changes. i. The perivascular infiltrations. The paucity of perivascular infiltrations is perhaps the chief objection to a diagnosis of epidemic lethargic encephalitis. These infiltrations are generally recognized as the most characteristic of the lesions. There is, however, to be found in the literature considerable support for the contention that the infiltrations are relatively slow in developing and consequently absent in the early stage of the disease. McIntosh¹⁷ is of this opinion on account of the histological appearance of the lesions and states that 'several acute cases where death has occurred within a week after the onset of the disease have shown only slight lesions in the brain.' Gay⁹ suggests that 'perivascular infiltration (cuffing) of mononuclear cells probably does not occur in the earliest stages.' Michels and Globus²³ observe that 'in cases of epidemic encephalitis that have run a stormy course with a sudden termination, the predominant histologic picture is that of numerous haemorrhages with an unusual sparsity of typical small round cell infiltrations.' McNalty²¹, referring to rapidly fatal cases, draws attention to the almost completely negative histological findings and the absence of perivascular infiltrations, which he attributes to the fatal issue having occurred before characteristic lesions had time to declare themselves. Duzar and Balo⁵, basing their opinion on post-mortem findings in the Budapest epidemic, express the view that characteristic infiltrations are found only in cases of relatively long duration. Kinnear Wilson³¹ describes perivascular infiltration consisting of only a few cells—'less than one complete layer round'—a description which aptly applies to the venule illustrated from case 1 of our series (fig. 2). In our cases the duration of the illness was very short, and perivascular infiltration was at an early stage of development.

ii. Haemorrhage. Reference has already been made (p. 165) to the importance of haemorrhages as a feature distinguishing encephalitis lethargica from poliomyelitis. Zinsser³⁴ describes them as perhaps the most striking element and states that some pathologists suspect haemorrhages to be the primary lesion.

iii. Changes in the nerve cells. The degenerative changes in the nerve cells found in our cases correspond closely to those described by McIntosh¹⁷ and others. The focal distribution of these changes which was so conspicuous is a characteristic already emphasized by Freeman⁸.

Experiments on animals. The results of Dr. Alston's attempts to transmit infection to animals of various species were negative. This is similar to the experience of the majority of those who have attempted experimental transmission of the virus of epidemic encephalitis. McIntosh and Turnbull¹⁷ succeeded in infecting a monkey with material from one of McNalty's cases, and Levaditi¹⁷ claimed success with rabbits, but his results were criticized on account of the likelihood of contamination of the inoculated material with herpes virus. Zinsser³⁴ even goes so far as to suggest that the successful transmission of infection in McNalty's case throws doubt upon the diagnosis.

Diagnosis.—From the clinical point of view these cases almost certainly represented an outbreak of acute encephalitis of epidemic nature. In such an isolated epidemic it was not possible to classify the cases as of any one particular form. Even pathologically, although the condition was clearly acute encephalitis, the findings were not absolutely conclusive as to type. Both clinically and pathologically these cases had many points of resemblance to several of the recorded types of acute encephalitis occurring as epidemics. These types have so much in common with each other that it is possible that they do not in reality represent separate entities, but are rather different manifestations of a single disease process. In the present state of knowledge, our findings would appear to indicate that our cases most closely resembled the lethargic type of epidemic encephalitis (von Economo) in an early stage.

Source of infection.—The almost simultaneous occurrence of the four cases seems to indicate a common source of infection rather than case to case transmission. No member of the staff in attendance on the four children reported sick at any time during the month of July. There were no other recognized cases of epidemic encephalitis in the wards. Apart from the possible presence of an unrecognized carrier there is little likelihood that infection was derived from any member of the staff or patient in the wards.

A possible source of infection existed in adult patients with post-encephalitic Parkinsonism with whom the children had associated. The possibility of infection arising from contact with cases of chronic encephalitis has been considered by several authorities. Both Netter²⁴ and Freeman⁷ favour the view that the later manifestations of the disease are due to the continued presence of the infective agent. Hall¹¹ considers that the occurrence of recrudescence at long and varying intervals provides clinical evidence of persistent infection. There is general agreement that the disease may be contagious in the initial acute stage. Netter and Freeman are definitely of this opinion. According to Hall, although proof is rare 'contagion may occur to a marked degree.' If it be recognized that the infective agent persists during the later chronic stage, the possibility of the disease being still contagious must be admitted. Netter recorded several cases in support of this view. These cases have been included in a review of the subject

by Freeman⁷, who collected seven cases of acute encephalitis which had developed in individuals who had been in close association with patients suffering from the disease in its chronic stage. These observers are inclined to relate the contagion in these cases to exacerbations occurring long after the original attack.

The infection in the cases of our two adult patients with chronic encephalitis dated from acute attacks nine and eleven years before. There was no history of any exacerbation in either case, but it may be mentioned that one of the patients had suffered from an attack of unexplained vomiting shortly before the outbreak among the children. The intimate contact occurring between these patients and the affected children has already been emphasized. On the assumption that the cases of chronic encephalitis lethargica were still infective, the risk of the children contracting infection could hardly have been greater.

If these chronic cases were the source of infection it can be definitely stated that the incubation period in the children was not more than two weeks, as there was no contact between the parties prior to July 7, 1933. McNalty²⁰, basing his estimate on records at the Ministry of Health, considers that the incubation period of encephalitis lethargica varies from two days to over two weeks.

It is not possible to dogmatize regarding the probable route of infection, but the presence of faecal and pharyngeal catarrh in every case suggests that the virus gained entry through the mucous membrane of those regions. There is considerable evidence favouring the view that the salivary secretion of patients suffering from chronic encephalitis is infective.¹¹ The condition of our adult patients was characterized by excessive salivation. As already mentioned, these women frequently fondled the children and actually kissed them. Under these circumstances it seems probable that infection entered by the fauces.

Summary.

The subject of the paper is a small outbreak of acute encephalitis in a hospital, affecting four young children, with two deaths. Clinical details are given, together with the results of examination of the blood and cerebro-spinal fluid. Autopsies were performed on the two fatal cases and full histological examination was carried out. Attempts were made to transmit the infection to animals. Various possibilities in connection with diagnosis are considered. The findings appear to indicate that the cases most closely resembled the lethargic type of epidemic encephalitis. The children had been in close contact with cases of post-encephalitic Parkinsonism. The possibility of infection from this source is discussed.

Acknowledgments.—We wish to express our thanks to Professor Charles McNeil, director of the Children's Unit, Western General Hospital; to Dr. W. T. Benson, superintendent of the City Fever Hospital, for allowing us to follow up the two cases which were transferred to his

charge; to Lieutenant-Colonel W. F. Harvey and Dr. W. O. Kermack, of the Royal College of Physicians laboratory, who examined the cerebro-spinal fluids; to Dr. I. G. McCrie, who provided us with clinical details concerning the cases of post-encephalitic Parkinsonism; and to Dr. W. D. Henderson, house physician, and Sister M. I. Campbell, without whose whole-hearted co-operation the clinical investigation of the cases could not have been carried out.

REFERENCES.

1. Boyd, W., *Canad. Med. Ass. J.*, Montreal, 1933, XXIX, 541.
2. Brain, W. R., & Hunter, D., *Lancet*, Lond., 1929, i, 221.
3. Brown, C. L., & Symmers, D., *Am. J. Dis. Child.*, Chicago, 1925, XXIX, 174.
4. Clelland, J. B., & Campbell, A. W., *J. Nerv. & Ment. Dis.*, New York, 1920, LI, 137.
5. Duzar, J., & Balo, J., *Jahrb. f. Kinderh.*, Berlin, 1922, XCIX, 209.
6. da Fano, C., & Ingleby, H., *Proc. Roy. Soc. Med.*, Lond., 1918-19, XII (Sect. Path.), 42.
7. Freeman, W., *J. Am. Med. Assoc.*, Chicago, 1926, LXXXVII, 1601.
8. Freeman, W., *Neuropathology*, Philadelphia, 1933.
9. Gay, F. P., 'Infections of the Central Nervous System,' *Ass. Res. Nerv. & Ment. Dis.*, Baltimore, 1932, XII, 194.
10. Grinker, R. R., & Stone, T. T., *Arch. Neurol. & Psychiat.*, Chicago, 1928, XX, 244.
11. Hall A. J., *Epidemic Encephalitis*, Bristol, 1924.
12. Holt, L. E., & Howland, J., *Diseases of Infancy & Childhood*, Lond., Ninth Edition, 1926.
13. *International Comm. for the Study of Infantile Paralysis*, Baltimore, 1932.
14. Leake, J. P., *J. Am. Med. Assoc.*, Chicago, 1933, CI, 928.
15. Low, A. A., *Arch. Neurol. & Psychiat.*, Chicago, 1930, XXIII, 697.
16. McCordock, H. A., *Bull. St. Louis Med. Soc.*, St. Louis, 1933, XXVIII, 10.
17. McIntosh, J., *System of Bacteriology in Relation to Medicine*, Lond., 1930, VII, 169.
18. McIntosh, J., & Turnbull, H. M., *Brit. J. Exper. Path.*, Lond., 1920, I, 89.
19. McNalty, A. S., *Rep. to Loc. Gov. Board on Pub. Health and Med.*, Sub. N.S., 1918, No. 121.
20. McNalty, A. S., *Epidemic Diseases of the Central Nervous System*, Lond., 1927.
21. McNalty, A. S., *Annual Report of Chief M.O., M. of Health*, Lond., 1919-20, App. VII.
22. Report of Matheson Commission, *Epidemic Encephalitis*, New York, 1929 & 1932.
23. Michels, N. A., & Globus, J. H., *Arch. Path.*, Chicago, 1927, IV, 692.
24. Netter, A., *Bull. et mém. Soc. méd. d'hop. de Paris*, Paris, 1920, XLIV, 1030.
25. Netter, A., *ibid.*, 441.
26. Price, G. E., *Am. J. Med. Sci.*, Philadelphia, 1922, CLXIII, 871.
27. Raimist, J., quoted by Hall, A. J., *Epidemic Encephalitis*, Bristol, 1924.
28. Riley, H. A., *Arch. Neurol. & Psychiat.*, Chicago, 1930, XXIV, 574.
29. Strauss, I., Rabiner, A. M., & Ginsburg, S. W., *Infections of the Central Nervous System*, Baltimore, 1932.
30. Syllaba, I., & Henner, K., *Arch. Int. Med.*, Chicago, 1928, XLII, 151.
31. Wilson, S. A. K., *Lancet*, Lond., 1918, ii, 7.
32. Winnicott, D. W., & Gibbs, N., *Brit. J. Child. Dis.*, 1926, XXIII, 107.
33. Zentay, P. J., *Bull. St. Louis Med. Soc.*, St. Louis, 1933, XXVIII, 4.
34. Zinsser, H., *Arch. Path.*, Chicago, 1928, VI, 271.

THE AETIOLOGY OF IDIOGLOSSIA

BY

I. J. WOLF, M.D.,

Associate Paediatrician, Barnet Hospital, Paterson, N.J.

The term idioglossia was introduced by Hale White and Golding Bird¹ in 1891 to describe a defective condition of speech in two brothers aged ten-and-a-half and nine years respectively, which gave the impression of an individual language. Idioglossia may be defined as lalling or dyslalic speech which is so extreme in degree as to render it incomprehensible to the ordinary listener. A parent or one accustomed to hearing it spoken by a particular child may learn to comprehend it; but the idioglossic speech of another child will not necessarily be understood without study. Various authors have attributed this speech manifestation to:—

1. a faulty perception of speech, the child merely repeating the sounds as he hears them (McReady²);
2. a faulty motor co-ordination of articulation due to a brain defect of the motor speech centre (Hadden³, Thomas⁴);
3. a faulty motor co-ordination of articulation secondary to defective intelligence (Wyllie⁵); and
4. a faulty auditory perception due to faulty development of the auditory speech centre (Kerr⁶, Guthrie⁷, Worster-Drought and Allen⁸).

These various theories suggest that idioglossia has a varied aetiology, which will be seen to be the case on careful analysis. Recently, however, Worster-Drought and Allen have attempted to establish the thesis that idioglossia is peculiar to congenital auditory imperception (congenital word-deafness) and that those cases reported in the literature in the past fifty years which have been ascribed to other causes have been erroneously interpreted. They have attempted to discredit such aetiological factors as motor articulatory inco-ordination and mental deficiency, assuming that the latter, for instance, was the result of deprivation rather than the exciting cause.

This stand has influenced Morison⁹ and the Barton-Halls¹⁰ to believe that idioglossia is characteristic of congenital auditory imperception alone. Further, it has led these writers into reporting certain cases as congenital auditory imperception which do not belong in this category. For instance, the Barton-Halls reported three cases of idioglossia as cases of congenital auditory imperception, one of which certainly was a case of motor dyslalia and another possibly due to mild mental retardation.

Idioglossia is manifest in the speech of children other than those afflicted with congenital auditory imperception. It is the purpose of this paper to outline the varied aetiology of idioglossia and to show that it is merely a stage

in the development of speech whether this be normal or delayed. The stages of speech development in the normal child may be outlined here.

The first step is crying which is initiated reflexly at birth. Changes in temperature, sudden shifts in position, pain and hunger cause the infant to express his general feeling tone by means of different cries. By the second month usually, in moments of comfort, the infant discovers spontaneously many primitive sounds such as gurgling, cooing and crowing, which are comparable to the reflex cries described to express his unpleasant states of feeling tone. They are produced by accidental, inco-ordinated movements of the muscles of articulation as a result of simple motor discharges. A persistence of the motor patterns laid down associated with pleasurable moments cause the infant to indulge in repetitions.

About the age of eight to ten months, the infant begins to perceive simple and then more complex sounds which he tries to imitate in a meaningless fashion known as echolalia. The associations made between sounds perceived and objects seen, felt and smelled is the basis for the comprehension of speech. The first associations are primitive relating to affective states of hunger, pain and pleasure, and the timbre of voice. Then the infant learns to appreciate the meaning of the combination of sounds comprising words. When an infant responds correctly to an acoustic impression, one may say that he has acquired the understanding of the spoken word. Coincident with the comprehension of speech is the appreciation of facial expressions and gestures.

The comprehension of speech is acquired long before the acquisition of articulate speech, although the infant uses the cry and other sounds to express himself when he has not words at his command. The time comes when he consciously associates a word uttered with its object. If he calls his mother, he associates the word with her and does not repeat it without meaning. This is used as the criterion for the onset of speech; it is usually observed at about the age of one-and-a-half years, although many children reach this stage sooner.

At this point the idioglossic stage of speech development begins. The child tries to reproduce the speech he hears, but a lack of skill in articulation causes him to be dyslalic. In the beginning this is so marked that his utterances are incomprehensible, except for words that are repeated singly. This stage may be termed physiological idioglossia. Slowly his articulation becomes more clear and he passes into a stage of universal dyslalia which is characterized by omissions and reductions, reduplications, assimilations, metatheses, etc. Similar phenomena are observed in the development of languages and dialects as the result of various influences to bring about phonetic change. The same causes are operative to produce these phenomena in the speech of the child as in all spoken language. The fact that the child's articulatory experience is limited makes his speech more labile to these influences. As his skill in articulation increases, the number of faulty articulations decrease. By the third year he is able to express himself clearly in a simple manner. One or two single sound defects may persist for a longer time constituting a partial dyslalia. This term is used in contradistinction to universal dyslalia which denotes a more universally defective speech.

The child in his normal acquisition of speech is seen to pass through the following stages of development:—

1. Crying.
2. Babbling, or the articulation of primitive sounds.
3. Echolalia, or the meaningless repetition of sounds.
4. Comprehension of speech.
5. Acquisition of speech: a. idioglossia, b. universal dyslalia, and c. partial dyslalia.

Retarded speech development.—For the normal development of speech an intact speech arc must exist. The organs of sight and hearing, the auditory and motor memory centres, the cerebral cortex and the various pathways connecting these areas and organs must be intact. Interruption

of the arc at any point interferes with the development of speech. If the infant is congenitally deaf, or hearing is lost before speech is well established, deaf mutism results. If hearing becomes impaired due to otitis media or meningitis, speech is improperly received and faulty reproduction ensues. If mental deficiency exists, the child has not the cortical capacity to acquire speech, or speech is delayed in onset and development. If the auditory or motor memory centres are congenitally affected, auditory or kinesthetic speech memories cannot be stored properly. Psychological factors may exist to prolong the development of speech. The causes of retarded speech development may be given as follows:—

1. Psychological factors.
2. Impaired hearing.
3. Mental retardation.
4. Congenital auditory impereception (congenital word-deafness).
5. Congenital articulatory dyskinesthesia (motor dyslalia).

The speech manifestations of retarded lingual development are the same as those of normal lingual development. The stages of development of the lingually retarded child are also comparable to those of the child whose lingual development is normal. The distinction lies in the time of onset of speech and the time required to accomplish normal speech. Depending on the cause, normal speech may never be acquired. In the extreme degree, speech may not advance beyond the stage of primitive sounds or animal-like noises. In less severe cases, speech may remain idioglossic, dyslalic or partially dyslalic. The following examples illustrate the various stages of retarded lingual development that may be observed in mentally deficient children. Comparable stages of development may be observed in any case of retarded lingual development irrespective of the cause.

A child who showed severe mental retardation and was classed as an idiot only understood a few simple commands and expressed his wants and dislikes by means of primitive cries and sounds. Another whose mental retardation was less severe was able to repeat words in a meaningless fashion (echolalia). The speech he uttered was more or less unintelligible (idioglossia); his comprehension of speech was better than in the former case. A child with an even milder degree of mental deficiency understood speech well but his speech was dyslalic. With training his speech became defective only in the articulation of single sounds (partial dyslalia).

The stages of retarded lingual development then range between mutism and normal speech and may be enumerated as follows: the articulation of primitive sounds, echolalia, idioglossia, universal dyslalia and partial dyslalia.

Manifestations of idioglossia.—The speech manifestations of retarded lingual development in any given stage are the same as those of normal lingual development in any comparable stage. The lingual phenomena of physiological idioglossia and pathological idioglossia therefore are the same. Inasmuch as idioglossia is merely a heightened form of dyslalia, a consideration of the manifestations of dyslalia¹¹ will suffice. The following lingual phenomena will be observed: omission and reduction, substitutions, reduplication, assimilation, metathesis and analogy.

1. **OMISSION AND REDUCTION** are characterized by the omission of sounds and syllables from words, usually the difficult sounds and unaccented syllables. For instance, 'boom' is said for 'broom'; 'g'ome' for 'go home'; 'pa-bu' for 'pocket-book.'

2. **REDUPLICATION** consists in the repetition of simple syllables to form words. For instance, 'moo-moo' is said for 'cow'; 'bow-bow' for 'dog.' These particular words imitate the sound of the thing indicated.

3. **ASSIMILATION.** The child who says 'poom' for 'spoon' demonstrates assimilation combined with omission. Assimilation is the modification of one sound by another related in position or physiology. Thus 's' is omitted from 'spoon,' and 'n' is labialized to become 'm' to conform to the labial sounds 'oo' and 'p.'

4. **SUBSTITUTION.** The various sounds comprising the velar, labial and palatal groups are related in their mode of articulation. To one inexperienced in making these sounds substitutions are common. Those most frequently seen are: d for g (do for go); t for k (tat for eat); d or t for th (dis for this; tree for three); f for th (free for three); b for v (bery for very); and w for r (wun for run). The following sentence demonstrates omissions of sounds and sound substitutions. 'Do 'ome an' ta' free tats wif oo' for 'go home and take three cats with you.'

5. **METATHESIS.** Another manifestation of dyslalia is metathesis, which consists in the transposition of sounds or syllables in a word, or the transposition of words in a sentence. An example of transposition of sounds in a word is 'hopsital' for 'hospital.'

6. **ANALOGY.** Finally there is analogy which is the confusion of words due to a similarity in form, meaning or syntax (enemy for anemone; learn for teach; foots for feet), or the creation of new words or the application of new meanings to words by analogous association. Thus 'burneator' for 'radiator'; 'splinters' for 'moustache.'

Analysis of cases.

Physiologic idiglossia. Naomi S., aged 1½ years, comprehended speech well and used words with full comprehension of their meaning. These were more or less easily recognized if spoken singly. Otherwise her speech was idiglossic and quite unintelligible depending upon her loquacity. Especially at play one heard a flow of gibberish. During the following months, as her articulatory experience increased, a more normal speech began to evolve, and during this stage one was able to observe more readily the characteristic phenomena of dyslalia. Omissions and reductions, sound substitutions and metatheses were common.

Idiglossia due to mental retardation. Dorothy E., aged 3. The mother of this child suffered from severe eclampsia during pregnancy and labour had to be induced. The infant was slow in sitting up and walking. At the age of three, speech was idiglossic although words might be articulated more or less clearly if her attention could be maintained. She repeated words and phrases that she heard in a meaningless fashion. Comprehension of speech was fairly good. Observation of her speech showed that she dropped the endings of words, assimilated, substituted and omitted sounds in order to simplify speech.

Idiglossia due to impaired hearing. Mary T., aged 7, was a normal infant at birth. At the age of eight months she had a bilateral purulent otitis media which discharged for more than six months. She sat up at six months and walked at a year. During infancy her parents noticed that she paid no attention when spoken to, but it did not occur to them that her hearing was impaired. When she went to the hospital for diphtheria, they were told she did not hear. Her speech was mostly gibberish and she resorted to pantomime. She understood her mother, probably

reading her lips. She has learned to say 'mother' and 'daddy' and several other words. 'Frances' was said as 'Fwances,' 'pretty' as 'pwetty,' 'silver' as 'sturber,' 'singae' as 'didac' or 'stigda.'

Kinesthetic idioglossia. An idioglossic child may be observed who is intelligent, whose comprehension of speech has developed normally, but whose articulation has remained faulty beyond the normal physiologic limits of three years. Such a child is not dysarthric, nor is the speech defect dependent on any peripheral organic defect of the organs of articulation. The fault lies probably in the motor speech area; this type of case may best be described by the term 'articulatory dyskinesthesia.' Doris Van S., aged 4, is a case in point. She was an intelligent child whose developmental history was normal as was the onset of speech. Comprehension of speech had always been good. Her speech was incomprehensible except to her mother. On analysis one observed the characteristic manifestations of dyslalia, notably sound substitutions. for instance, 'berry' was said for 'very'; 'wove' for 'love'; 'tat' for 'cat'; 'do' for 'go'; 'tit' for 'sit'; etc.

Idioglossia due to auditory imperception. Lastly, there is idioglossia due to congenital auditory imperception, which is comparable to the idioglossia just described in the motor sphere.

The diagnostic criteria in these cases are:—

1. Normal intelligence.
2. Normal hearing.
3. Failure to comprehend the meaning of words and often crude sounds.
4. Idioglossic or dyslalic speech.
5. The ability to acquire speech through motor and visual channels, such as lip reading.

A case of congenital auditory imperception reported by Morison⁹ may be cited. Wilfred C., aged 13, whose intelligence and hearing were normal, comprehended speech by lip reading. His own speech was idioglossic. 'Saturday night' was said as 'Tatur nigh,' 'September' as 'Temtember' (t substituted for s in both these examples). 'Quarter past' said as 'tartar-tast' (t substituted for the k sound, and t used for p in 'past' by progressive assimilation). 'Basket' was said as 'bassie' (k assimilated to s and t omitted). Note that although t was substituted for s as in Temtember indicating an inability to articulate s, the ability to articulate this sound was shown in bassie for basket.

Comment.

Idioglossia then is a condition of speech reflecting the result of various influences to bring about phonetic change. Normally a faulty perception of new sound combinations and an articulatory inexperience combine to make the speech produced by the child in the first stages of speech acquisition idioglossic. As has been pointed out certain pathologic conditions may exist to interfere with the normal development of speech. The lingual phenomena observed are fundamentally the same. Cases of idioglossia or dyslalia, irrespective of the cause, reported by others may be studied and will be seen to display these lingual manifestations: omission and reduction, reduplication, assimilation, sound substitutions, metathesis, etc. Studying the speech defect in any given case will give no clue in itself to the underlying cause of the lingual defect. A history and examination of the patient along various lines will lead one to come to some conclusion concerning the nature

of the retarding factor. This position has been admitted by Allen¹², yet he would have us believe that true idioglossia is associated only with an inability to appreciate the meaning of word-sounds. In other words he says a defective condition of speech simulating idioglossia is observed under other circumstances than congenital auditory imperception, but these must be cases of spurious idioglossia. True idioglossia is characteristic of congenital auditory imperception alone but there is no means of distinguishing it from other forms of idioglossia by a study of the speech itself.

Summary.

Idioglossia is dyslalie speech so extreme in degree that it is incomprehensible to the ordinary listener. It is merely a stage in the development of speech whether this be normal or retarded. Its manifestations are the same as those of universal dyslalia: omission and reduction, reduplication, assimilation, metathesis, etc. Retarded lingual development of which idioglossia is a manifestation is due to impaired hearing, mental deficiency, articulatory dyskinesthesia and congenital auditory imperception. The idioglossia in these cases may be termed pathological idioglossia to distinguish it from the idioglossia of normal speech development or physiological idioglossia.

REFERENCES.

1. Hale White, W., & Golding-Bird, C. H., *Med.-Chir. Trans.*, Lond., 1891, LXXIV, 181.
2. McCready, E. B., *Am. J. Psychiat.*, Baltimore, 1926, VI, 267.
3. Hadden, W. B., *J. Ment. Sc.*, Lond., 1891, XXXVII, 96.
4. Thomas, C. J., *Pub. Health*, Lond., 1908, XXI, 90.
5. Wyllie, J., *Disorders of Speech*, Edin., 1894, 127.
6. Kerr, J., *Brit. Med. J.*, Lond., 1900, i, 1231.
7. Guthrie, L., *Functional Nervous Disorders in Children*, Lond., 1907.
8. Worster-Drought, C., & Allen, I. M., *J. Neurol. & Psychopath.*, Lond., 1930, X, 193.
9. Morison, A. G., *loc. cit.*, 28.
10. Barton Hall, S., & Barton Hall, M., *ibid.*, 1931, XI, 304.
11. Wolf, I. J., *J. Med. Soc. New Jersey*, Orange, 1934, XXXI, 156.
12. Allen, I. M., *Brit. J. Child. Dis.*, Lond., 1932, XXIX, 98.

THE INTRADERMAL TUBERCULIN REACTION

with special reference to so-called surgical tuberculosis*

BY

J. W. E. CORY, M.A., M.D. CANTAB.,
Hon. Surgeon, West Suffolk General Hospital.

The special interest of this paper centres around diseases of bones and joints and particularly the early diagnosis of tuberculosis of the hip joint. Tuberculosis of the hip presents a difficult problem; if the diagnosis is only made on definite text-book signs much valuable time may be wasted, yet if a provisional diagnosis is made early in the disease some non-tuberculous conditions will be included. There seems little doubt that it is better to begin treatment at once even at the expense of occasionally treating as tuberculous such conditions as coxa plana, slipped epiphysis or subacute septic arthritis of the hip.

In certain cases in spite of expert observation, good skiagrams and pathological investigations it is impossible to make a definite diagnosis for several months. The opening of the joint and demonstration of the tubercle bacillus is not always justified and the septic may point at the successfully cured cases and ask for proof that they were tuberculous.

As this early treatment of hip disease by immobilization in hospital is a serious step involving discomfort to the child, loss of schooling and a considerable expenditure of public funds, it is necessary in addition to a very careful clinical examination to collect all evidence which will assist.

I have used the intradermal tuberculin test since the beginning of 1928 and the results obtained until August, 1931, are used in this communication. More recent cases have not been used as their ultimate diagnosis may need revision.

The intradermal test was introduced by Mantoux¹ working in Paris in 1908 and by Mendel in Berlin in the same year. Mantoux injected into the layers of the skin of the forearm the equivalent of 0.01 mgm. of old tuberculin prepared by the Pasteur institute. He claimed that the technique of injection was as easy as giving an hypodermic injection and described the results as follows: 'Immediately after injection there is a small "boule d'oedema," which becomes absorbed and reappears after some hours as a raised papule. Later it becomes visible either white or rose coloured and in twenty-four hours is red in colour and around it is a white oedematous granite-like surface, and further outside this a rosy halo. In forty-eight hours it reaches its maximum and begins, as a rule, to subside, the size varying from a 50 centime piece to a 2 franc piece. The skin remains cool, but there is some tenderness on pressure.'

* Based on a thesis accepted for the degree of M.D. Cantab.

The method of obtaining the necessary dilutions is simple. A 1 in 100 solution is made by adding 0.5 c.c. of old tuberculin to 50 c.c. of normal saline and using for injection 0.1 c.c. of this solution, equivalent to 1 mgm. A 1 in 1,000 solution is obtained by adding 1 c.c. of the above solution to 9 c.c. of normal saline; here 0.1 c.c. is equal to 0.1 mgm. The control solution is obtained in the same way using glycerin broth instead of the tuberculin; the normal saline is sterilized and has 0.25 c.c. of pure carbolic acid in each 100 c.c.

In carrying out a series of tests by the Mantoux method, it has been found better to use two glass syringes, one for the injection of the tuberculin and the other for the controls. These are best sterilized by boiling and allowing them to dry before using and washing through with ether after use. In a few cases in which the same syringe was used for tuberculin and for the control solution, the control arm gave a very slight reaction. Even with careful use a small trace of the tuberculin may be left in the shoulder of the syringe or in the upper end of the needle.

The syringes used were white glass ones graduated in tenths of a cubic centimetre with a well-fitting coloured glass piston, supplied by Messrs. Allen and Hanbury. The needles were No 18 stainless steel, soft metal, with a rather short bevel.

The control arm has usually been injected first as it shows the child there is nothing to fear and should a mistake be made owing to the child moving, the injection can be repeated. For this, the right forearm is used after being washed with soap and water and swabbed with ether. When the arm is dry the skin is stretched by holding the forearm tightly with the left hand and the injection is made with the right. The needle is introduced almost parallel to the skin with the bevel of the needle showing as it enters the skin; when the bevel opening has disappeared into the layers of the skin the needle is turned so that the bevel faces deeply: 0.1 c.c. of the fluid is introduced and forms a small raised papule about $\frac{1}{16}$ in. across. The injection is made easier if the needles are kept in liquid paraffin when not in use, as even after boiling a fine film of paraffin remains and facilitates the introduction into the skin. The same technique is used for the injection of the tuberculin except that in most cases the left forearm is used.

Results.

A certain amount of experience is required to interpret the results. In a few cases in which the same syringe was used for the control and for the injection through a different needle, a small circular patch of erythema appeared on the control arm. In a few non-tuberculous cases a small circular patch of erythema about $\frac{1}{4}$ in. in diameter appeared on both arms. This was regarded as negative if slight, or indefinite if the reaction was greater in the test arm than in the control.

The size of the reaction varies somewhat in different states of the disease, but no prognostic significance is attached to the reaction in the present paper. The response is more marked in the stronger dilutions than in the weak. In 20 tuberculous cases injected both with 1 in 100 dilution and with 1 in 1,000 dilution, the reaction to the stronger dose, measured 2 days later, varied from $\frac{1}{4}$ in. to 3 in. making an average wheal of just over $1\frac{1}{4}$ in. in diameter, while in the weaker dilution the reaction varied from $\frac{1}{8}$ in. to $1\frac{1}{2}$ in., the average being a little over $\frac{1}{2}$ in. In a further series of twelve tuberculous cases injections were made simultaneously with dilutions of 1 in 250 and 1 in 2,500; the stronger solution gave a wheal of from $\frac{3}{8}$ in. to $1\frac{1}{2}$ in. the average being 1 in., while in the weaker dilution the reaction varied from a negative to $\frac{3}{8}$ in., the reactions being mainly too small to measure.

In thirty-two cases of tuberculosis the temperature was specially noted every four hours for three days after injection. Of those injected with 1 in 100 dilution, six ran a temperature above their usual level, the evening rise varying from 0.2° F. to 2.4° in one case; the remaining 14 were not affected.

Of twelve injected with a weaker dilution of 1 in 250 only two were mildly affected: in one the evening temperature which was usually 99° rose to 99.2° , while in another, normally afebrile, it rose to 99° .

I have never seen any ill-effects from an initial dose of 0.1 c.c. of 1 in 100 dilution of the tuberculin. On the other hand, I consider that 1 in 1,000 dilution is too weak for general use because in patients who are definitely tuberculous, but not seriously ill, this dilution gives such a weak response as to be inconclusive.

The results obtained in the few cases in which 1 in 250 dilution was used were very satisfactory and it is possible that this is the optimum dilution for the more chronic cases.

In three cases negative reactions were obtained with the weaker dilution although the patient was tuberculous and gave a positive response to the higher concentration.

The 243 cases here discussed are with five exceptions, children under 12 years of age. They are collected from the Hospital for Sick Children, Great Ormond Street, the Wingfield Orthopaedic Hospital, Headington, Oxford, the West Suffolk General Hospital, Bury St. Edmunds, and from private practice.

To facilitate discussion it is essential to group the cases and the classification adopted by Moncrieff² in his article on the interpretation of the intradermal test has been adopted as eminently satisfactory.

GROUP 1.—DISEASES OF BONES AND JOINTS.

	Age		Total.
	under 7.	over 7.	
Number of tuberculous cases giving a positive reaction	16	30	46
Number of suspected tuberculous cases giving a positive reaction and subsequently proved tuberculous ...	1	—	1
Number of suspected tuberculous cases giving a negative reaction and subsequently proved to be non-tuberculous	5	4	9
Number of apparently non-tuberculous cases giving a positive reaction ...	2	1	3
Number of tuberculous cases giving a negative reaction	—	—	—
Number of non-tuberculous cases giving a negative reaction	19	15	34
Indefinite cases	2	1	3
	45	51	96

Diseases of the bones and joints (96 cases).—This is one of the most important groups and the reaction has been more accurate than in any of the other groups except possibly of glandular affections. It is interesting also because many of these children were observed over a longer period of time, varying from three months to five years, and consequently the ultimate diagnosis has been more firmly established. It was unfortunate that in Moncrieff's² article on the interpretation of the intradermal reaction in which he has discussed its uses very fully he has only two cases of diseases of bones and joints; a fact which he himself comments on.

Of the 96 cases of affections of bones and joints, 46 were almost indisputably tuberculous and gave a positive Mantoux reaction. The clinical diagnosis was aided by a series of skiagrams and in many instances was further supported by the demonstration of tubercle bacilli or typical tuberculous tissue. These fall into the following divisions:—

Tuberculous hip	25
Tuberculous spine	15
Tuberculous knee	1
Tuberculous ankle	1
Tuberculous dactylitis	1

and in three cases the spine was involved with a second lesion in the hip, knee or wrist.

Thirty-four patients not considered to be suffering from tuberculosis gave negative reactions. These can be classified as follows:—

Congenital talipes	5
Mastoiditis	13
Spina bifida	3
Osteomyelitis	3
Sarcoma of spine	2
Fracture	2

and one case each of the following, coxa plana, osteochondritis of the femur, spastic diplegia, anterior poliomyelitis, multiple exostoses and congenital absence of the coccyx. These do not require much comment except to point out that if they had been tested before the diagnosis was established the reaction would have helped in elucidating the condition in the case of the coxa plana and of osteochondritis of the femur. Sarcoma of the spine is a relatively rare condition and a negative reaction would have reminded the observer of the possibility of sarcoma. These cases were not selected, but occurred in the course of a series of tests performed in hospital wards. No cases of proven tuberculosis in this group failed to react to the injection of tuberculin. This is a very significant point as it does not hold good in some of the other groups.

In one case, a boy of 2½ years, was admitted with a synovitis of the knee, which was not considered to be tuberculous. The Mantoux reaction was positive and at the end of a month in hospital he was considered to be tuberculous independently of the skin reaction.

Nine cases suspected of being tuberculous were under observation at the time the test was performed and gave a negative result. Two of these were cases of synovitis of the knee in boys of five and six respectively. They were treated by immobilization and by removal of all septic foci. In one case there was a biopsy of the knee joint and microscopic examination of the synovia. In neither case was any evidence of tuberculosis found, nor were there any bone changes. Both made a perfect recovery in a few months. They were considered to be of subacute septic origin, in one case the focus being the tonsils. Another case, aged 3½ years, was admitted at a very early stage of hip joint disease, which was at first thought to be tuberculous, but which was proved by opening the joint on the sixth day to be due to an acute streptococcal infection. Two cases were difficult cases of subacute septic arthritis of the hip joint which quickly recovered after immobilization and the removal of septic foci. A boy of 12 was treated as tuberculous, but at a subsequent review six months later was thought to be suffering from a staphylococcal infection of the hip joint and the subsequent history of the case supported this view. Another case had multiple lesions of finger, knee and ankle joints, which were at first treated as tuberculous, but later proved to be a polyarthritis of septic origin.

In 1928, C. S., 5 years old, was in hospital as a case of tuberculosis of the right hip, the radiogram showing two foci in the head of the femur. I considered at the time that the Mantoux test in giving a negative reaction had failed, but in December, 1931, I wrote to Mr. G. R. Girdlestone, who replied—‘the subsequent history of C. S. confirms the Mantoux tuberculin diagnosis. Apparently the result has been so satisfactory that there is a strong suggestion that the condition has never been tuberculous. . . . the clinical course has been more suggestive of a non-tuberculous infection.’

The same is true of V. C., 7 years old, who was being treated for tuberculosis of the left hip joint. He was reviewed by Mr. W. B. Foley also working at Oxford in 1932, who writes:—‘. . . got full restoration of movements of the hip joint. His series of x-rays when I came to review them, I thought were rather more suggestive of slipped epiphysis than tuberculosis, and I think you will be fully justified in regarding him as non-tuberculous.’

Three cases who were not at the time being treated for tuberculosis gave positive reactions. One case of acute mastoiditis in a girl of three and a half years, who had in addition a gonococcal vaginal discharge had no obvious signs of tuberculosis, but nothing was known of the family history. Two other cases, one of arthritis of the temporo-mandibular joint in a girl of four and another in a boy of five with bilateral talipes equino-varus gave positive reactions. Both the children had spent a large part of their lives in hospital wards, but beyond this fact there is no adequate explanation of the tuberculous tendency. In none of these cases were skiagrams of the chest taken or any investigations made beyond a thorough clinical examination.

Three cases gave ‘doubtful reactions.’ In one case, R. G., with club feet, a mild reaction occurred both in the injected arm and also in the control arm showing that either the needle was not sterile or the child was sensitive to the protein of the media used both for the tuberculin and also for the control. H. H., a case of mastoiditis, gave a negative control and a slight reaction occurred in the arm into which the tuberculin was injected, but the reaction was so slight that it could not be classified as a positive. R. L. gave a very slight reaction in the control arm and a positive reaction in the arm used for tuberculin injection both in 1 in 100 and in 1 in 1,000 dilution. At the time he was thought to have a tuberculous hip, but five years later there is still some doubt as to whether or not the condition is tuberculous.

GROUP 2.—ABDOMINAL CONDITIONS.

	Age		Total.
	under 7.	over 7.	
Number of tuberculous cases giving a positive reaction	6	2	8
Number of suspected tuberculous cases giving a positive reaction and subsequently proved tuberculous ...	—	1	1
Number of suspected tuberculous cases giving a negative reaction and subsequently proved to be non-tuberculous	1	1	2
Number of apparently non-tuberculous cases giving a positive reaction ...	—	2	2
Number of tuberculous cases giving a negative reaction	2	—	2
Number of non-tuberculous cases giving a negative reaction	20	2	22
Indefinite cases	1	—	1
	—	—	—
	30	8	38
	—	—	—

Abdominal conditions (38 cases).—Eleven of the thirty-eight patients in this group suffered from some form of abdominal tuberculosis and nine of them reacted to the test. The two who did not react were very ill at the time of injection, one (J. L.) died less than a fortnight afterwards and at necropsy an enormous mass of caseating mesenteric glands was found; the other although very ill was removed from hospital by the parents. It is probable that both these cases would have reacted to a stronger dose of tuberculin. Happ and Casparis³ in their paper on the value of the intracutaneous tuberculin reaction in extensive tuberculosis state that they believe a failure to react to the tuberculin in miliary tuberculosis is due to a depression and not to complete loss of sensitiveness to tuberculin and that if high enough concentration is used a positive result can be obtained in practically all cases of tuberculosis. In the present series a larger dose than 0.1 c.c. of a 1 in 100 dilution of tuberculin has not been used because in those cases in which a lower dose gave a negative reaction, the diagnosis had already been established and therefore from a clinical standpoint the excessive dose was not justified.

In abdominal tuberculosis it might be argued, that, as the infection may have originated from infected milk bovine tuberculin should be tried. Tisdall and Brown⁴ in their series of 159 cases never found a case which reacted to bovine tuberculin, and which did not respond to human tuberculin. Gaisford⁵ used human and bovine tuberculin for a number of the 500 cases in his series and found no differences in their reaction. Tytler⁶ working on animals found the results were the same whether he used human or bovine tuberculin. He attributes the apparently weaker reactions of the bovine tuberculin to the more scanty growth of the culture from which the diluted tuberculin is prepared. He makes another interesting observation, perhaps worthy of comment here, that human cases, which react to human

or bovine tuberculin do not react to avian tuberculin or at most no more than to *bacillus coli* or other organisms. He considers it to be non-specific.

Twenty-two cases of abdominal disease not considered as tuberculous gave negative results. Two cases of abdominal disease not considered tuberculous gave positive reactions; one, A. D., suffering from acute streptococcal salpingitis was living with her mother, who had active pulmonary tuberculosis; the other, a boy of 11 years, was suffering from appendicitis, and had no signs of tuberculosis, or history of contact with tuberculous persons.

Two cases at the time of injection were under observation as tuberculous and gave negative reactions, the one proved to be a case of congenital idiopathic dilatation of the colon and the other a case of recurrent appendicitis. One case, A. J., gave a positive reaction, but was discharged without a diagnosis being made. One case, P. S., aged 11 years, seen in April, 1931, is worthy of comment; after influenza at his preparatory school during the previous term he developed a slight malaise with anorexia, loss of weight and an evening temperature between 99° and 100°. Just before his return home an attack of abdominal pain suggested the possibility of appendicitis. Careful clinical examination revealed nothing except a soft cardiac bruit, which had been noted two years previously; the urine and stools were normal both in appearance and on pathological examination. The blood count was somewhat suggestive of tuberculosis: R.B.C. 5,600,000, haemoglobin 72 per cent., colour index 0.64, W.B.C. 6,250; polymorphonuclear 32 per cent.; eosinophil 0.33 per cent.; basophil 1.33 per cent.; lymphocytes 61.34 per cent.; large hyaline 5.0 per cent.

A Mantoux reaction was positive and under an anaesthetic some hard abdominal glands were felt under the right costal margin confirming the diagnosis of early abdominal tuberculosis. After three months in bed in the open air he made an excellent recovery.

GROUP 3—INTRACRANIAL CONDITIONS.

	Age		
	under 7.	over 7.	Total.
Number of tuberculous cases giving a positive reaction	—	2	2
Number of tuberculous cases giving a negative reaction	1	1	2
Number of non-tuberculous cases giving a negative reaction	5	—	5
	—	—	—
	6	3	9
	—	—	—

Intracranial conditions.—In the present series this group is too small to be of much practical use, but it bears out what other observers have found, that the test is of little value in these conditions. A negative result in a normal dilution of the fluid is of no value in excluding tuberculosis and would not help in deciding between a case of meningococcal meningitis and one of tuberculous meningitis.

Of the nine patients in this group four were cases of tuberculous meningitis and two gave positive reactions, the other two who gave negative reactions died shortly afterwards, and post-mortem examination showed typical tuberculous meningitis. The remaining five patients not being treated as tuberculous gave negative results.

GROUP 4.—FEBRILE CONDITIONS.

	Age under 7.	Age over 7.	Total.
Number of suspected tuberculous cases giving a negative reaction and subsequently proved to be non-tuberculous	1	—	1
Number of tuberculous cases giving a negative reaction	1	—	1
Number of non-tuberculous cases giving a negative reaction	3	—	3
	—	—	—
	5	—	5
	—	—	—

Febrile conditions.—There are only five patients in this group, as many of the febrile cases naturally fall into one or other of the remaining seven groups. All five gave negative results: in two of these the test was useful in helping to exclude tuberculosis as the cause of an abscess in one case in the axilla and in the other in the groin. J. D. was at the time of injection suffering from miliary tuberculosis and did not respond; at post mortem the diagnosis of miliary tuberculosis was confirmed, signs of tuberculous meningitis being the most evident.

One case of typhoid fever gave a negative result during the febrile stage: the test was not repeated as perhaps it should have been to illustrate a point emphasised by Mitchell⁷, working in America, who found that a positive reaction of the skin to tuberculin is approximately two to four times as frequent during the convalescent, afebrile stages of such diseases as measles, diphtheria, scarlet fever, varicella, poliomyelitis, pneumonia and gastro-enteritis as it is during the febrile stages of these diseases. In general hospital work one does not see many of these cases on whom it is justifiable to perform the test and in private practice it has not been done for obvious reasons.

GROUP 5.—GLANDULAR AFFECTIONS.

	Age under 7.	Age over 7.	Total.
Number of tuberculous cases giving a positive reaction	9	9	18
Number of suspected tuberculous cases giving a positive reaction and subsequently proved tuberculous ...	1	—	1
Number of non-tuberculous cases giving a negative reaction	3	—	3
Indefinite cases	—	1	1
	—	—	—
	13	10	23
	—	—	—

Glandular affections.—Of the twenty-three children in this group eighteen were straightforward cases of tuberculous adenitis, giving positive results with the diagnosis confirmed at operation. The test helped to reveal the cause of a retropharyngeal abscess of tuberculous origin and it is note-

worthy that in three cases of septic adenitis the test was negative. One case who gave a positive reaction is classified as doubtful. He had a sinus in the neck, which was at first regarded as tuberculous and treated as such for a year. A diagnosis of branchial fistula was then made and excision performed, but as no microscopic examination of the tissue was made, the actual pathological condition must remain uncertain.

GROUP 6.—URINARY AFFECTIONS.

		Age		
		under 7.	over 7.	Total.
Number of tuberculous cases giving a positive reaction	—	1	1
Number of apparently non-tuberculous cases giving a positive reaction	...	2	1	3
Number of non-tuberculous cases giving a negative reaction	7	5	12
Indefinite cases	1	—	1
		<hr/>	<hr/>	<hr/>
		10	7	17
		<hr/>	<hr/>	<hr/>

Urinary affections.—Only one case of the sixteen in this group was frankly tuberculous and gave a positive reaction. Twelve cases, five of pyelitis, four of nephritis, one of cystic kidney, one of sarcoma of the kidney and one of cystitis gave negative results.

Three cases gave positive reactions without showing any clinical signs of tuberculosis. One was a boy with cystitis and a congenital abnormality of the membranous urethra and the other two were cases of nephritis. These three cases were not considered to be suffering from tuberculosis and no special investigations were made to exclude latent or healed infection of mediastinal glands. It is possible that the kidney condition in the two cases of nephritis was tuberculous for the tubercle bacilli are notoriously difficult to demonstrate, but that view was not held at the time of injection and the patients have since been lost sight of.

GROUP 7.—CHEST CONDITIONS.

		Age		
		under 7.	over 7.	Total.
Number of tuberculous cases giving a positive reaction	1	3	4
Number of apparently non-tuberculous cases giving a positive reaction	...	1	1	2
Number of non-tuberculous cases giving a negative reaction	8	3	11
		<hr/>	<hr/>	<hr/>
		10	7	17
		<hr/>	<hr/>	<hr/>

Chest affections.—In this group of seventeen patients four who were definitely tuberculous gave positive results, while eleven, who were not suspected of being infected gave negative results. Of the two remaining

cases, one child suffering from broncho-pneumonia gave a positive reaction, she came of a tuberculous family, but it is uncertain whether she was actually in contact with open tuberculosis. Dow and Lloyd⁸ working on tuberculous infection and its relation to contagion in children find that the incidence of a positive skin reaction in the first five years of life is five times greater in those who are in contact at home with open tuberculosis than in those who are not so exposed. The other case giving a positive reaction was one of asthma, but showed no signs of tuberculosis. The reaction did not appear to be due to a hypersensitivity of the skin to the protein of the media as the control was negative. In this connection it is interesting to note that Storm van Leeuwen and Varekamp⁹ working at Leiden found that most of their asthma patients reacted strongly to tuberculin with the von Pirquet test.

GROUP 8.—MISCELLANEOUS CASES.

	Age		Total.
	under 7.	over 7.	
Number of suspected tuberculous cases giving a positive reaction and subsequently proved tuberculous ...	1	1	2
Number of apparently non-tuberculous cases giving a positive reaction ...	3	5	8
Number of non-tuberculous cases giving a negative reaction	23	6	29
	—	—	—
	27	12	39
	—	—	—

Miscellaneous cases.—Of the thirty-nine remaining patients not included in the other groups none were at the time of injection diagnosed as tuberculous, but in two the positive reaction obtained helped to elucidate the condition. One was an unusual ulcer of the palate in a child aged eight months, which presented considerable difficulty in diagnosis, later some secondary glands appeared in the neck and microscopic section showed their tuberculous character. The other child was in hospital for the repair of a hare lip and cleft palate and was further investigated as a result of the positive intradermic reaction. An x-ray of the chest showed well-marked calcified peribronchial glands. Dow and Lloyd¹⁰ find that calcified peribronchial glands are frequent with a positive Mantoux reaction, but appear to attach very little significance to the finding. Twenty-nine children suffering from various non-tuberculous conditions gave negative reactions. There remain eight children, who gave positive reactions without at the time suffering from active tuberculosis.

A child, aged 5 years, was being treated for erythema nodosum and gave a very strongly positive skin reaction. This is interesting in view of a recent paper by W. R. F. Collis¹¹ who records the frequency of a positive skin reaction to tuberculin in erythema nodosum. Mackenzie believed that erythema nodosum was rheumatic in origin, while other observers have pointed out its association with tuberculosis. Collis believes that both these observations are correct in that both the tuberculous and the streptococcal infections play an important part. He suggests that erythema

nodosum is a type of hyper-reactive tissue response to various bacterial allergens and that the allergens responsible for erythema nodosum in London are commonly the tubercle bacillus and the haemolytic streptococcus.

E. S., a child aged 8 months, admitted as a case of marasmus was the ninth child of a father, who had undefined 'lung trouble,' the whole family of eleven living in two slum rooms. There were definitely enlarged glands present in both sides of the neck, which were probably tuberculous.

E. K., 10 months old, was admitted with a provisional diagnosis of anaemia and was, after investigation, diagnosed as suffering from tuberculous meningitis. There was a low erythrocyte count of only two million, the leucocyte count showed only 4,600 cells of which 66 per cent were lymphocytes: at post mortem nothing was found to confirm the diagnosis which must therefore remain uncertain.

A case of scleroderma and one of multiple deformities gave positive skin reactions as also did two cases of chorea and one case of rheumatism. The association between tuberculosis and the rheumatic diseases has been pointed out, but it is beyond the scope of this article to enter into a discussion of this interesting subject.

Discussion.

From the preceding analysis it would appear that the test is definitely more useful in the so-called "surgical" than in the medical forms of tuberculosis. Taking the whole series, 84 tuberculous cases gave positive skin reactions and 131 non-tuberculous cases gave negative reactions. In 17 cases the skin test was negative and the tentative diagnosis had to be revised, while in another 17 cases the skin test was positive without tuberculosis being the cause of the pathological condition for which the patient was under treatment; in five cases of tuberculosis the test was negative.

Analysing these cases from another aspect it will be found that of 136 children under twelve, who were not at the time under treatment for tuberculosis 119 (87.5 per cent.) gave negative results. Of these 136 children 95 were under 7 years old and in this age group 88 (92.6 per cent.) gave negative results. Of 41 children between 7 and 12 years of age 31 only (75.6 per cent.) gave negative results. Schlesinger and Hart¹² found in 1930 among hospital out-patients that one-fifth of the children under six years of age, not exposed to tuberculosis at home, gave positive skin reactions.

Of 89 tuberculosis cases 84 (94.3 per cent.) gave positive results; yet of 101 cases giving positive skin tests only 84 (84 per cent.) were tuberculous. Of the children under seven years of age 7 (4.8 per cent.) of a total of 145 children gave unexpected positives while between 7 and 12 years of age 10 (10 per cent.) out of 98 gave positive results, which were unexpected.

Conclusions.

The significance of a positive reaction.—The positive intracutaneous reaction means that the child has acquired a definite allergic reaction to the products of the tubercle bacilli and either has or has had tuberculosis. Children whose parents are tuberculous and who are exposed to open tuberculosis at home are much more liable to produce a positive reaction although they are not at the time suffering from active tuberculosis.

There seems to be little doubt that the younger the child the greater must be the significance attached to a positive result and that the older the child the less importance need be attached to it from a clinical aspect. The intradermal test, therefore, should never be allowed to establish a diagnosis of tuberculosis unless well supported by other evidence, but the test should take its place and a very useful place, in the balance of evidence for or against a diagnosis of tuberculosis.

The significance of negative reaction.—A negative skin reaction to an ordinary diagnostic dose of tuberculin (0.1 c.c. of 1 in 100 dilution) may mean:—

1. That the child has not been infected with tuberculosis.
2. That the test has not been properly performed or the tuberculin used is inactive.
3. That the child is already so ill with tuberculosis that its skin sensitivity is too much diminished to react.
4. That, although the child is suffering from tuberculosis, an intercurrent fever, such as measles has caused a temporary diminution of the skin sensitivity and that if repeated during convalescence a positive result may be obtained with the same dose.

The findings here reported agree with those of Mantoux who wrote in 1910 'A negative test except in measles, meningitis and miliary tuberculosis and advanced cases with marked toxæmia is an argument of the first order in excluding clinical tuberculosis; contrary to most clinical methods the value of the intracutaneous test lies in its negative results.'

Acknowledgments.—The author wishes to acknowledge with thanks the facilities put at his disposal by the Staff of the Hospital for Sick Children, Great Ormond Street, and especially Mr. O. L. Addison, Mr. L. E. Barrington Ward and Mr. T. Twinstington Higgins for the encouragement received. To Mr. G. R. Girdlestane he is very much indebted for permission to carry out tests upon children at the Wingfield Morris Orthopaedic Hospital, Oxford, and for being allowed to return at intervals to verify the diagnoses. He has also been allowed to test a certain number of patients under the care of the Staff of the West Suffolk General Hospital and he wishes to thank his colleagues for their co-operation.

REFERENCES.

1. Mantoux, C., *Compt. rend. Acad. d. sc.*, Paris, 1908, CXLVII, 355.
2. Moncrieff, A., *Quart. J. Med.*, Oxford, 1931, XXIV, 153.
3. Happ, W. M., & Casparis, H. R., *Am. J. Dis. Child.*, Chicago, 1922, XXIII, 527.
4. Tisdall, F. F., & Brown, A., *Canad. Med. Ass. J.*, Montreal, 1926, XVI, N.S., 939.
5. Gaisford, W. F., *Lancet*, Lond., 1931, i, 521.
6. Tytler, W. H., *System of bacteriology*, *Med. Res. Council*, Lond., 1930, V, 250.
7. Mitchell, A. G., *et alii*, *Am. J. Dis. Child.*, Chicago, 1928, XXXVI, 720.
8. Dow, D. J., & Lloyd, W. E., *Brit. Med. J.*, Lond., 1931, ii, 183.
9. Van Leeuwen, W. S., *Proc. Roy. Soc. Med.*, Lond., 1932, XXV, 1454.
10. Dow, D. J., & Lloyd, W. E., *Brit. Med. J.*, Lond., 1932, i, 701.
11. Collis, W. R. F., *Quart. J. Med.*, Oxford, 1932, N.S., 141.
12. Schlesinger, B., & Hart, D'A., *Arch. Dis. Childh.*, Lond., 1930, V, 191.

SENSITIVITY TO COW'S MILK PROTEINS IN ACUTE GASTRO- ENTERITIS

BY

K. H. TALLERMAN, M.C., M.D., M.R.C.P.

(From the Children's Department and the Hale Clinical Laboratory of the London Hospital.)

The high mortality of acute gastro-enteritis in infants makes urgent the problem of elucidating its exact causation and nature. Between the years 1927 and 1932, of 170 infants admitted under the care of the Children's Department of the London Hospital who suffered from this condition, 73 died, giving a mortality rate of 43 per cent. If the very mild cases are excluded from this series, the death rate becomes 77 per cent. These figures are not dissimilar to those occurring in most other hospitals.

The intestinal lesions found at autopsy in these cases—are as a rule not in themselves sufficient to account for death, and it is probable that they are frequently the result rather than the cause of the diarrhoea. Alimentary infection, often preceded by unsuitable feeding, is known to be frequently responsible for the onset of acute gastro-enteritis, but it is also recognized that in many cases gastro-enteritis is associated with a focus of infection—which many regard as primary—elsewhere than in the gastro-intestinal tract. In all severe cases, however, the symptoms show that there is dehydration of the body, and profound general toxæmia. Of the nature of this highly dangerous toxæmia there is still much that is unknown.

It appears that in conditions of marasmus and gastro-intestinal disturbances in infancy the secretion of gastric juice is decreased; there is also evidence that trypsin may be deficient in infants suffering from diarrhoea. It follows that digestion must be impaired and the breaking down of proteins interfered with. It has been shown by experiments that athreptic infants and those suffering from gastro-enteritis absorb undigested protein from their alimentary tracts (Schloss and Anderson¹, Anderson and Schloss², Schloss³); both by precipitin tests and by anaphylactic experiments on guinea-pigs, these workers demonstrated that antigenic protein was absorbed into the blood in such cases.

Moreover, experiments quoted by Schloss³, which were conducted by himself and his co-workers, showed that the enteral absorption of antigenic protein leads to specific skin hypersensitivity, as demonstrated by intradermal tests. Further, Greer⁴ demonstrated by means of intradermal injections that sensitivity to cow's milk occurred in infants suffering from acute gastro-

enteritis, whereas normal infants showed no such sensitivity. The reason for this absorption of protein in wasted infants and those suffering from acute gastro-enteritis cannot be definitely stated, but probably incomplete protein digestion and increased permeability of the alimentary tract are both factors involved. Theoretically it seems possible that the fatal toxicosis occurring in severe gastro-enteritis may be associated with this absorption of relatively large amounts of foreign protein unchanged. Such a possibility has already been suggested by Schloss³ and others. It seems significant that some of the symptoms of acute intoxication occurring in severe cases of gastro-enteritis are not unlike some of those seen in protein shock.

It has been shown by Schloss³ that normal infants fed on cow's milk absorb for a short time a certain small amount of the foreign protein of cow's milk unchanged, though this is infinitely less than in the case of wasted infants, or those suffering from diarrhoea. After the ingestion of foreign protein, normal infants produce very promptly an immunity reaction, as shown by precipitin formation. The precipitin is present in the blood, however, for a short time only, its subsequent disappearance showing that absorption of antigenic protein has probably then ceased. It is therefore reasonable to suppose that normal infants rapidly put themselves in a position to deal with such protein by the production of antibodies until the absorption ceases. If, however, an infant should happen to absorb more foreign protein than it is able to cope with in such a manner, it may become allergic to the protein, the body having established only a partial defence. Should the infant now suffer a gastro-intestinal upset, there is likely to be a sudden larger absorption by the unhealthy and more readily permeable alimentary tract of unaltered protein, which has been incompletely digested owing to a diminution of the normal supply of proteolytic ferments. It is possible then that an infant who is allergic to cow's milk protein is thus suddenly exposed to the absorption of a relatively large amount, and as a result severe allergic reactions occur, which may be to a great extent responsible for the toxic symptoms. In accord with such a theory is the fact that acute gastro-enteritis is much commoner in infants fed on cow's milk than in those that are breast fed, and is especially liable to occur after rapid weaning.

As a further step in the study of this problem it was therefore decided—assuming, on the basis of previous work, that foreign protein had been absorbed by those infants suffering from acute gastro-enteritis—to try and ascertain whether or not they had become sensitive to such foreign protein. With this in view an attempt was made to determine whether or not reagins were present in the blood of these infants, rendering them allergic to cow's milk. For this purpose the Prausnitz-Küstner reaction was employed. This consists in transferring sensitivity to a given antigen to the skin of a previously insensitive person, by means of an intradermal injection of serum from a subject himself allergic to this antigen. This passive transfer reaction would, if positive, show that reagins were present in the blood of the infants concerned, and thus demonstrate that they were sensitive to the antigen in question.

Experimental procedure.

About 5 c.c. of blood was taken from the superior longitudinal sinus of each of 18 infants under the age of 9 months, suffering from gastro-enteritis in the acute stage. The majority were severely ill, 11 dying within a relatively short time. No infant that was breast fed was included in the series, and all had, so far as it was possible to ascertain, received various types of cow's milk feeding only. No mixed feeding had been commenced, therefore any foreign proteins that might have been absorbed would be those of cow's milk only.

After withdrawal in a dry syringe, the blood was defibrinated by shaking with glass beads in a bottle, and then centrifuged. The serum was pipetted off, put up in ampoules ready for use, and stored in an ice chest. The Wassermann reaction was carried out on each child's serum; it was found to be negative in all cases.

The subjects on whom the test reaction was carried out were convalescent male patients whose general medical condition was good. As a preliminary to each experiment, the subject was skin-tested by the scratch method with an extract of whole cow's milk protein, in order to ascertain that he did not exhibit sensitivity to cow's milk. Prior to commencing the test, all milk was excluded from his diet for approximately 24 hours. An intradermal injection was then made, in the flexor surface of the upper arm, of 0.075 cc. of the infant's serum to be tested; in certain cases the serum had previously been diluted with saline, in others it was used undiluted. At first a 1 in 5 dilution was used, but it was soon decided to use a greater concentration. Twenty to twenty-four hours later, the sensitized site and a control site were each injected with 0.04 c.c. of antigen. The antigen used in most instances was a lactalbumin extract* (since it is known that sensitization is more commonly produced by lactalbumin than by casein), but in certain experiments whole, sterile cow's milk was employed.

After injection of antigen, readings were taken at the end of $\frac{1}{2}$ hour, 1 hour, 2 hours, 3 hours, and then again on the following day.

The serum utilized was, as already stated, obtained in the acute stage of acute gastro-enteritis. In practically every instance, more than one test was made with each serum; owing to the small quantities of serum available, it was not possible to test each serum both diluted and undiluted, and with each of the antigens mentioned.

The results of 42 Prausnitz-Küstner reactions, as carried out upon the above lines, are shown in the following table.

Discussion.

Admittedly the above investigation, carried out on a relatively small series of cases, is not conclusive, and in certain instances the results obtained from the injection of one serum into two different subjects were at variance. Of the 18 infants whose sera were tested, 8, however, gave completely positive results, while only 2 cases (1 and 6) gave consistently negative results. Five (cases 5, 9, 11, 14 and 15) gave results that were positive in one or more tests, but equivocal in others. The remaining 3 (cases 2, 8, and 12) gave contradictory results. Of the whole series of 42 Prausnitz-

* The lactalbumin extract employed was obtained from Messrs. Duncan Flockhart and Co.

	Serum diluted 1 in 5. Lactalbumin extract diluted 1 in 2.	Serum diluted 1 in 2. Lactalbumin extract diluted 1 in 2.	Serum diluted 1 in 2. Whole cow's milk.	Serum undiluted. Lactalbumin extract undiluted.	Serum undiluted. Whole cow's milk.
1. G. B.	-	-	-		
2. P. B.	+	-			
3. E. K.	++	+	(a) ++ (b) ++		
4. B. W.		+			
5. T. V.		(a) + (b) +			
6. R. C.		(a) - (b) -			
7. S. M.		(a) + (b) ++			
8. M. D.		(a) - (b) ++ (c) +	++		
9. J. W.			(a) + (b) +		
10. C. M.			(a) ++ (b) ++		
11. W. B.			(a) + (b) ++		
12. P. R.			+		(a) + (b) -
13. S. de B.				+	
14. J. S.				(a) + (b) + (c) + (d) +	
15. D. O.				(a) + (b) +	
16. R. P.				(a) + (b) +	
17. J. A.					(a) ++ (b) +
18. S. G.					(a) ++ (b) ++

The small letters (a), (b), etc., are used to indicate that more than one test was performed.

Küstner reactions carried out, 61.9 per cent. gave definitely positive results, and only 19 per cent. were definitely negative. This, especially when taken in connection with previous work already quoted, is significant. It may be noted that, although Greer¹ found that it was chiefly to lactalbumin that sensitivity occurred, the more strongly positive results were, generally speaking, obtained in the above experiments when whole cow's milk was employed as antigen.

Conclusions.

It appears from the experiments carried out that reagins to cow's milk proteins are frequently present in the blood of infants suffering from gastro-enteritis. From this one may conclude that many such infants are hypersensitive to cow's milk proteins.

It is possible that some of the toxic symptoms of acute gastro-enteritis may be in the nature of an allergic reaction.

It is a pleasure to acknowledge with thanks the valuable advice and helpful criticism received from Dr. S. P. Bedson throughout this work, and the assistance in the form of a grant from the Research Committee of the London Hospital.

REFERENCES.

1. Schloss, O. M., & Anderson, A., *Proc. Soc. Exper. Biol. & Med.*, Utica, 1922-23, XX, 5.
2. Anderson, A. F., & Schloss, O. M., *Am. J. Dis. Child.*, Chicago, 1923, XXVI, 451.
3. Schloss, O. M., *Harvey Lect.*, Baltimore, 1924-25, series XX, 156.
4. Greer, V. D., *Arch. Pediat.*, New York, 1917, XXIV, 810.

BRITISH PAEDIATRIC ASSOCIATION.

PROCEEDINGS OF THE SEVENTH ANNUAL GENERAL MEETING.

The Seventh Annual General Meeting was held at the Old England Lake Hotel, Windermere, on Friday and Saturday, the 27th and 28th April, 1934.

FIRST SESSION (APRIL 27TH, 10 A.M.).

Business Proceedings : The President, Dr. Eric Pritchard (London), was in the Chair, and there were present 53 members.

The minutes of the last Meeting were read and approved.

The following Officers, Honorary and Ordinary Members were elected.

President : 1934-35, Dr. J. Hugh Thursfield (London).

Secretary : Dr. A. Maitland-Jones (in place of Dr. Donald Paterson (resigned)).

Treasurer : Dr. H. Morley Fletcher (re-elected).

Representatives for Provinces : Dr. Hugh Ashby (Manchester) and Dr. Norman Capon (Liverpool).

Representative for London : Dr. Donald Paterson in place of Dr. A. Maitland-Jones.

Honorary Member : Dr. A. Dingwall Fordyce (Past President).

Ordinary Members : Dr. Reginald Lightwood (London), Dr. Basil J. Rennie (Glasgow), Dr. Howard Stewart (Belfast), Dr. A. G. Watkins (Cardiff).

Next Meeting : The selection of the next place of Meeting was left to the Executive Committee.

The Treasurer's Report was received and adopted.

It was proposed by Donald Paterson, seconded by K. D. Wilkinson, that 'Notwithstanding any rule to the contrary, distinguished Paediatricians who are resident outside the British Isles and the Free State, may be elected "Corresponding Members" on the nomination of the Executive Committee. The members elected shall not exceed 10 in 1934-35 and 2 in each subsequent year, and that Rule 2 should have added "and Corresponding Members." This was almost unanimously agreed to.

1. DR. J. S. Y. ROGERS (Dundee) : 'Partial reduplication of ureter.' He described a boy aged 12 years with recurrent abdominal pain for fully three years, solely relieved by rest in bed. The pain was referred to areas of D. 10, 11, 12 and L. 1. There were no clinical signs, the urine was normal. An x-ray with a plain film was negative. After intravenous injection of 15 c.c. Uroselectan B. the films revealed separate double kidney pelvis and partial double ureter. At operation: ligation and resection of upper branch. The speaker described varieties of anomalies of kidneys and ureters and discussed diagnosis and treatment.

In the present case a further pyelogram showed lower branch draining two lower calyces, upper calyx not functioning. The boy is in excellent health and free from pain.

2. DR. A. V. NEALE (Birmingham): 'A follow-up of some coeliac cases.' A review was made of eight cases of coeliac disease who had been under continued observation and treatment for eight years or more. Remarkably good results had been obtained with clinical and biochemical recovery. The ultimate stature and physique was good. Sexual function and development was normal. No anaemia. Mental state was good. Previous serious coeliac rickets with deformity had entirely cleared. The prolonged treatment was well worth the ultimate result.

3. DR. WILFRID Vining (Leeds): 'Remarks on a case of multiple arthritis and severe anaemia.' A case of a child aged 3½ years who, following a period of four months during which there was a striking anaemia in conjunction with glandular hyperplasia in the neck and axillae, developed a generalized symmetrical painful enlargement of his joints. Death followed at the end of seven months from the onset of his illness. At the post mortem an extensive deposition of biurate was found in the joints and subcutaneous tissues about the elbows and knees. Microscopic examination of the organs showed leukaemic infiltration of the kidney and liver. There was a family history of gout coming through the father's side, and it was suggested that this was a case of acute gout precipitated by lymphatic leukaemia. The blood at no time showed increase in the white cells and their relative proportion was not disturbed.

4. DR. W. W. PAYNE (London) introduced by DR. R. W. B. ELLIS: 'The acid metabolism in rheumatism.' Three groups of children of approximately 200 each were taken, one from a rheumatic clinic, one from an asthmatic clinic and one from a residential school. Urines passed on rising, after breakfast and before bedtime were collected and the acid, ammonia, phosphate, pH, etc., estimated. The pH showed no change from group to group. The rheumatic and asthmatic groups passed more acid than the normal group but the asthmatic group were receiving enough acid a day to account for the difference between them and the normal. As far as could be told there was no essential difference between the diets of the three groups.

It was concluded that the rheumatic group excreted more acid than either control group.

5. DR. WM. BROWN (Aberdeen): 'Calcium in the treatment of chorea.' In cases of chorea when other treatment had failed, large doses of calcium were given to test the sedative effect on the nervous system. Doses of 10 to 20 c.c. of calcium gluconate solution were given each day intramuscularly, followed after ten days by large doses of calcium by the mouth. Injections were painless and did not upset the patients. The effects were definitely favourable. In most cases the movements stopped very early, speech was regained and the children were able to feed themselves tidily. Early control was obtained over the emotions. Examples were shown of the hand-writing method of estimating the actual disappearance of the movements.

6. DR. J. V. C. BRAITHWAITE (Leicester): 'Sunlight and pink disease.' That sunlight has a causal relation to pink disease is indicated by its prevalence in sunny countries, its seasonal incidence in England, its predilection for the country and suburbs, and the bad effect of exposing patients to the sun (one patient died a few hours after unintentional exposure, and another showed signs of collapse). The condition is greatly ameliorated and the course of the disease is shortened by keeping the children away from sunlight. Blood diluted with saline and exposed to sunlight was haemolysed except when it was taken from anaemic patients. This occurred through glass as well as quartz. Ultraviolet light produced no haemolysis through glass, neither did white light from a 2 kilowatt lamp. Exposing the blood saline mixture to heat, however, produced haemolysis. At 52° C. blood was haemolysed less rapidly when obtained from a patient with pink disease than when it came from other children, but at 55° C. haemolysis occurred more rapidly. Blood

from children with pneumonia behaved in a similar way. It was therefore concluded that the noxious influence of the sun was due largely to heat, and this was confirmed by treating the condition by cold sponging, light clothing, etc. Two patients so treated were apparently well in a fortnight.

7. DR. R. C. JEWESBURY (London): 'Two cases of diaphragmatic hernia in infants.' The first case was a male child of 3½ months, admitted to hospital for dyspnoea and slight cyanosis since birth. The breathing was found to be worse after food. Breath sounds were absent in lower half of the right chest and intestinal sounds were heard in this area on one occasion. X-ray examination confirmed a hernia through the right half of the diaphragm. The child died a month later at home. The second case was a male child aged 4½ months. Dyspnoea was first noted after an attack of gastro-enteritis one week before admission to hospital. The heart was displaced to the right and breath sounds were absent over lower part of left side of chest. X-ray examination confirmed the diagnosis of left-sided diaphragmatic hernia, and an operation by Mr. Max Page was successfully performed through the abdominal route with repair of an orifice in region of left pleuro-peritoneal canal. The child lost all symptoms and the left lung re-expanded, but unfortunately death from intestinal obstruction occurred ten days later.

SECOND SESSION (APRIL 27TH, 8.30 P.M.).

8. DR. REGINALD MILLER (London), in opening a discussion on the use and abuse of infant welfare centres, said that the latest figures available to indicate the size of the movement related to the end of 1932. There were then 2,783 centres in England, including 218 in London. Of these 749 were under voluntary bodies and the rest under local authorities. Compared with the previous year the total number had increased by 32, the voluntary centres had diminished by 88 and the municipal increased by 120. In 1932 the number of children under one year attending for first time was 318,166, amounting to 57.8 per cent. of the notified births. He argued that the movement now showed all the hall-marks of bureaucratic control, and that the right people to be in charge were those experienced in paediatrics and not those specially instructed in public health. His own view of the movement could be summed up in Whistler's dictum on Wilde: "He has no enemies, but his friends dislike him very much."

He was followed by DR. WILFRID Vining (Leeds) and DR. K. D. WILKINSON (Birmingham). A discussion followed in which several speakers took part including DR. C. MCNEIL (Edinburgh), DR. HECTOR CAMERON (London), DR. LEONARD FINDLAY (London), and the PRESIDENT, DR. ERIC PRITCHARD.

9. DR. K. D. WILKINSON showed a series of cinematograph films.

THIRD SESSION (APRIL 28TH, 10 A.M.).

10. DR. D. W. WINNICOTT (London): 'Inhibition of feeding in infancy and early childhood.' From psycho-analysis of adults it has long been clear that the feelings of infants and toddlers are much more intense than would appear, and that they can, and commonly do produce serious symptoms. Recently, psycho-analysis of small children has directly confirmed these findings. The speaker had opportunity of studying a moderately severe feeding inhibition in his analysis of a girl of three years (150 hours, over six months), and he found, as others doing this work have found, that it is the unconscious (repressed) phantasies that interfere with physiological functions. In this case the inhibition, which was soon accompanied by other symptoms, appeared at 12 months, and at first was related to feeding in the presence of both parents. As the analysis proceeded, release of the physiological function closely followed the child's increasing ability to tolerate the appropriate phantasies and feelings in consciousness.

11. DR. DONALD BATEMAN (London), introduced by DR. DONALD PATERSON: 'The use and technique of continuous intravenous saline in the treatment of dehydrating and intoxicating disorders in infancy.' A method of treating dehydration and intoxication in infants by means of continuous intravenous saline was described. The indications for the treatment were persistent vomiting and diarrhoea giving rise to dehydration. Such conditions were usually met with in gastro-enteritis, acute obstruction, post-operative vomiting and a variety of other diseases. The solution to be administered was 5 per cent. glucose in saline or 5 per cent. glucose in Hartman's solution. The apparatus for administration was described and also a special continuous intravenous needle (made by Messrs. Allen & Hanbury, to specifications). The control of the apparatus was outlined and a system of after-feeding presented. It was suggested that the treatment had certain advantages over subcutaneous saline and single intravenous saline infusion and that it should be used when the given indications arose.

12. DR. ALAN MONCRIEFF (London): 'Treatment of intracranial damage in the new-born.' He pointed out that the commonest findings in neonatal death are oedema and congestion of the brain and that an increased intracranial pressure is probably the main factor in causing death. Experimental work and clinical experience with hypertonic salt solutions intravenously or into the bowel demonstrate that increased intracranial pressure can be reduced. The method at present employed has been to give enemata of 2-3 oz. of 10 per cent. common salt solution. This is given with the minimum of disturbance and repeated as required until symptoms abate. Other ancillary methods are employed at the same time. Over an experience of twenty cases the impression has been gained that this is a life-saving measure.

13. DRs. WILFRID SHELDON AND B. A. McCANCE (London): 'Bone and vegetable broth.' Analysis of the mineral content of bone and vegetable broth showed it to be inferior to milk, especially as to calcium, phosphorus and iron. There was no advantage in adding a weak acid such as vinegar. The protein of the broth consisted entirely of gelatin. The salts from bones and vegetables did not continue to be extracted after the first hour, and while cooking was essential to obtain the salts from vegetables this was not so in the case of the bones. Except for the extraction of gelatin, an equally valuable broth (as regards mineral content) could be obtained by soaking bones for an hour in cold water, and then adding vegetables and cooking for an hour.

14. DRs. J. C. HAWKSLEY, REGINALD LIGHTWOOD AND W. W. PAYNE (London): 'Observations on acholuric jaundice.' In familial acholuric jaundice changed morphological and physical properties of the erythrocytes would appear to be fundamental. Morphologically there is increased thickness and diminished diameter of the cells (spherocytosis); this change was observed on the second day of life in the infant of an affected family, although no symptoms of the disease appeared until five weeks later. Similarly, the physical cell-abnormality (increased fragility) was present on the second day in the same case. The fragility 'trait' is known to be transmitted as a Mendelian dominant. The effects of splenectomy on these two erythrocyte phenomena of acholuric jaundice are:— 1. The mean diameter moves towards the normal and may then revert. 2. The fragility likewise shows slight temporary improvement. Pathologically, the main histological changes are due to increased erythrocyte destruction and to increased erythropoiesis. The volume of the evidence favours the view of an inborn error of erythropoiesis but the changes subsequent to splenectomy appear to show that the spleen plays more than a passive part.

15. DR. J. B. RENNIE (Glasgow): 'Nephritis in infancy.' During three years 10 cases of acute nephritis in infants under 18 months occurred, giving an incidence of 5.5 per cent. of all cases of acute nephritis in children under 13 years. All the cases showed massive oedema attributable to the great reduction of serum proteins which occurred. Syphilis was not a causal factor. Owing to the liability to

secondary infection, the prognosis was grave, seven of the cases dying from that cause. In three cases recovery from nephritis was apparently complete. Attention is drawn to the fact that all the cases showed the nephrotic type of nephritis.

16. DR. R. W. B. ELLIS (London): 'Hepatic infantilism.' Five examples of hepatomegaly glycogenica (von Gierke's disease) were described, characterised by great hepatic enlargement, from 4 to 8 years' infantilism, a low resting blood sugar, and a delayed rise in blood sugar following the injection of adrenalin. The condition is generally regarded as due to an inability to mobilize liver glycogen, which is stored in excessive amount. It was suggested that the infantilism was the result of long-standing tissue starvation of carbohydrate, shown by the low resting blood sugar values, and was analogous to Payne's observation that diabetic children fail to grow if over-treated with insulin.

17. DR. H. C. CAMERON (London): 'Unusual sites of tuberculosis infections.' He recorded the case of an infant 8 months' old suffering from acute tuberculous laryngitis, whose father had been removed three weeks before to a sanatorium. The earliest symptom was aphonia followed by gradually increasing stridor. On admission, three weeks after the father's removal, there was dullness and bronchial breathing of a very obvious character at the right apex. Laryngoscopic examination showed ulceration of the larynx. The x-ray showed apical tuberculosis of the right lung. Laryngeal obstruction developed, and a month after admission the child's condition was so distressing that tracheotomy had to be performed, and death followed five days later. At the post mortem there was caseous tuberculosis of the apex of the right lung with tuberculous ulceration of the true and false cords of the larynx. The mediastinal and bronchial glands were not involved in the tuberculous process.

He also recorded two cases in young children in both of which the early symptoms had given rise to a confident diagnosis of anterior poliomyelitis—a short pyrexial period followed by loss of power in one leg with loss of knee jerk and wasting of the muscles below the knee. In both cases, after a transitory improvement, some three weeks' later, the children developed tuberculous meningitis which, after the usual course, proved fatal. At the autopsy in the second case examination of the spinal cord showed tuberculous lymph surrounding the issuing nerve roots of the lumbar plexus. On section there were numerous giant cells and areas of caseation.

18. DR. G. B. FLEMING (Glasgow): 'Five cases of cyst of the lung.' All the cases were examples of single lung cyst. In four the cysts contained air and in one, fluid. Three died and two aged 1½ years and 8 years respectively, are apparently healthy. There were post-mortem examinations in two of the cases. In one the cyst was lined by ciliated columnar epithelium and in the other by flattened epithelium. From the cyst containing fluid, ciliated columnar epithelial cells were recovered. Three of the patients with air-containing cysts gave physical signs closely resembling pneumothorax. Paracentesis and withdrawal of air relieved symptoms temporarily in two of the cases.